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(54) Title: METHODS OF TREATING FUNGAL INFECTIONS WITH INHIBITORS OF NAD SYNTHETASE ENZYME

(57) Abstract: The present invention provides methods of treating or preventing fungal infections in a host comprising administering a treatment effective or treatment effective amount of a yeast NAD synthetase inhibitor compound. The invention further provides a method of killing yeast comprising administring a yeast NAD synthetase compound that selectively binds to catalytic sites in yeast whereby the yeast is killed.

METHODS OF TREATING FUNGAL INFECTIONS WITH INHIBITORS OF NAD SYNTHETASE ENZYME

CROSS REFERENCE TO RELATED APPLICATIONS

This application is related to copending provisional application Serial No. 60/141,436, filed June 29, 1999, which is incorporated by reference, and claims the benefit of its earlier filing date under 35 USC Section 119(e).

FIELD OF THE INVENTION

The present invention relates to methods of treating fungal infections. More particularly, the present invention relates to methods of treating yeast infections with compounds that selectively target the NAD synthetase enzyme of yeast, with little or no attendant targeting of the NAD synthetase enzyme of the host.

BACKGROUND OF THE INVENTION

The incidence of serious fungal infections, either systemic or topical, continues to increase for plants, animals, and humans. Fungi are plant-like eukaryotes that grow in colonies of single cells, called yeasts, or in filamentous mutlicellular aggregates, called molds. While many fungi are common in the environment and not harmful to plants or mammals, some are parasites of terrestrial plants and others can produce disease in humans and animals. When present in humans, mycotic (fungal) diseases can include contagious skin and hair infections, noncontagious systemic infections, and noncontagious foodborne toxemias. The incidence of such infections is not insignificant; in the U.S. approximately 10% of the population suffers from contagious skin and hair infections. While few healthy persons develop life-threatening systemic fungal infections, immunocompromised individuals, such as found in pregnancy, congenital thymic defects, or acquired immune deficiency syndrome (AIDS), can become seriously ill. This is further illustrated by the fact that fungal infections have become a major cause of death in organ transplant recipients and cancer patients.[1]

Numerous antifungal agents have been developed for topical use against nonsystemic fungal infections. However, the treatment of systemic fungal infections, particularly in immunocrompromised hosts, continues to be a major objective in infectious disease chemotherapy. The organisms most commonly implicated in systemic infections include *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp., although there are a number of emerging pathogens. The major classes of systemic drugs in use currently are the polyenes (*e.g.*, amphotericin B) and the azoles (*e.g.*, fluconazole). While somewhat effective in otherwise healthy patients, these agents are inadequate in severely immunocompromised individuals. Furthermore, drug resistance has become a serious problem, rendering these antifungal agents ineffective in some individuals.[2,3]

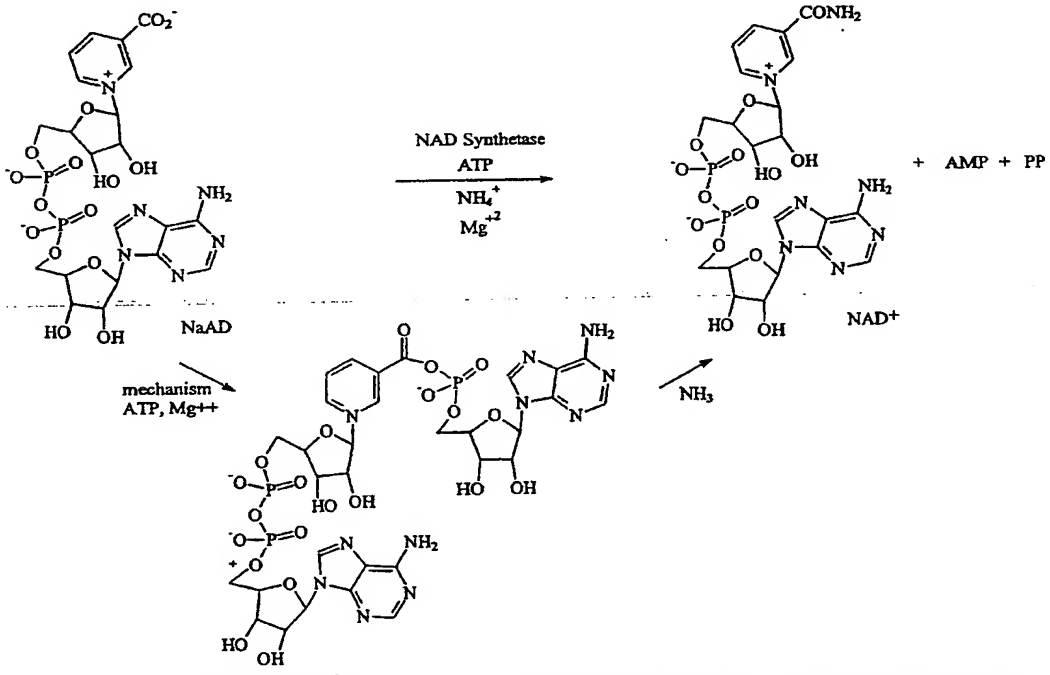
One reason for the limited number of systemic antifungal agents relates to the fact that, unlike bacteria, which are prokaryotes, yeast and molds are eukaryotes. Thus the biochemical make-up of yeast and molds more closely resembles eukaryotic human and animal cells. In general, this has made it difficult to develop antifungal drugs which selectively target in yeast an essential enzyme or biochemical pathway that has a close analog in humans and animals.

The ability to selectively inhibit the yeast form of a biochemical target with minimal effect on the mammalian form would provide a number of new approaches to the development of systemic antifungal drugs. In a few cases, this type of approach has already been proven to provide clinically useful systemic antifungal agents. For example, the mechanism of action for fluconazole, a widely used systemic antifungal drug, involves inhibition of a fungal C-14 demethylase, a cytochrome P450 enzyme that is essential for the production of the principal fungal sterol ergosterol. Ergosterol is very similar to the mammalian steroid cholesterol, and there is a closely related mammalian C-14 demethylase enzyme for which fluconazole is a much poorer inhibitor. This selectivity for inhibition of the fungal form of the enzyme over the mammalian form has resulted in the clinical utility of fluconazole.[4] In a further

example, preclinical studies on new antifungal agents that select for the yeast form over the mammalian form of a biochemical target include development of inhibitors for the plasma membrane ATPase[5] and for topoisomerase I.[6]

The inventors herein previously were part of a group that developed a number of antibacterial and antimicrobial agents that were targeted to NAD synthetase, an essential enzyme found in nearly all prokaryotic and eukaryotic cells. This enzyme is essential for the biosynthesis of nicotinamide adenine dinucleotide (NAD^+), an essential cofactor in numerous enzymatic reactions. NAD synthetase catalyzes the last step in both the *de novo* and salvage pathways for NAD^+ biosynthesis, which involves the transfer of ammonia to the carboxylate of nicotinic acid adenine dinucleotide (NaAD) in the presence of ATP and Mg^{+2}. The overall reaction is illustrated in Scheme 1.

Scheme 1



Prokaryotic NAD synthetase is an ammonia-dependent amidotransferase that belongs to a family of "N-type" ATP pyrophosphatases; this family also includes

asparagine synthetase and argininosuccinate synthetase.[7] Unlike eukaryotic NAD synthetase found in yeast and mammals that can use glutamine as a source of nitrogen, the prokaryotic NAD synthetase of bacteria requires ammonia as the only nitrogen source. Furthermore, *B. subtilis* NAD synthetase, which was previously crystallized and used for drug design by the inventors, is a dimer with molecular weight around 65,000, while the yeast enzyme is multimeric and has at least 10 times larger molecular weight.[8] These differences between eukaryotic and prokaryotic forms of NAD synthetase enzyme suggested that drugs specific for the prokaryotic enzyme could be designed, and the inventors subsequently developed inhibitors of this enzyme that are effective antibacterial and antimicrobial agents.[9] Given these marked differences between prokaryotic and eukaryotic NAD synthetase, the inventors fully expected that the compounds would be selective for the prokaryotic NAD synthetase and would show little to no effect on eukaryotic NAD synthetase.

SUMMARY OF THE INVENTION

The present invention is based in part on the surprising discovery that NAD synthetase inhibitors are highly effective in inhibiting the growth of yeast, yet exhibited only moderate toxicity in animals. Thus, the present invention includes the use of NAD synthetase inhibitors as new antifungal agents for preventing or controlling parasitic yeast and mold infections in plants, and for the prophylactic or therapeutic treatment, topically and systemically, of fungal infections in humans and animals.

In a major aspect, the present invention provides a method of treating or preventing an antifungal infection in a host comprising administering to a host a treatment effective or treatment preventive amount of a yeast NAD synthetase enzyme inhibitor compound.

In a further aspect, the method of killing yeast with an amount of yeast NAD synthetase enzyme inhibitor to reduce or eliminate the production of NAD whereby the yeast is killed.

In yet another aspect, the invention provides a method of decreasing yeast growth, comprising contacting the yeast with an amount of a yeast NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby yeast growth is decreased.

Additional advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

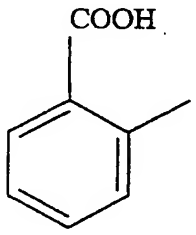
The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included herein.

Before the present methods, compounds, compositions and apparatuses are disclosed and described it is to be understood that this invention is not limited to the specific synthetic methods described herein. It is to be further understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly,

when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Throughout this application, where a chemical diagram has a straight line emanating from a chemical structure, such a line represents a CH_3 group. For example, in the following diagram:



o-methylbenzoic acid is represented.

The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. The term "cycloalkyl" intends a cyclic alkyl group of from three to eight, preferably five or six carbon atoms.

The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be defined as -OR where R is alkyl as defined above. A "lower alkoxy" group intends an alkoxy group containing from one to six, more preferably from one to four, carbon atoms.

The term "alkylene" as used herein refers to a difunctional saturated branched or unbranched hydrocarbon chain containing from 1 to 24 carbon atoms, and includes, for example, methylene (-CH2-), ethylene (-CH2-CH2-), propylene (-CH2-CH2-CH2-), 2-methylpropylene [-CH2-CH(CH3)-CH2-], hexylene [-(CH2)6-] and the like. The

term "cycloalkylene" as used herein refers to a cyclic alkylene group, typically a 5- or 6-membered ring.

The term "alkene" as used herein intends a mono-unsaturated or di-unsaturated hydrocarbon group of 2 to 24 carbon atoms. Asymmetric structures such as (AB)C=C(CD) are intended to include both the E and Z isomers. This may be presumed in structural formulae herein wherein an asymmetric alkene is present.

The term "alkynyl" as used herein refers to a branched or unbranched unsaturated hydrocarbon group of 1 to 24 carbon atoms wherein the group has at least one triple bond.

The term "cyclic" as used herein intends a structure that is characterized by one or more closed rings. As further used herein, the cyclic compounds discussed herein may be saturated or unsaturated and may be heterocyclic. By heterocyclic, it is meant a closed-ring structure, preferably of 5 or 6 members, in which one or more atoms in the ring is an element other than carbon, for example, sulfur, nitrogen, etc.

The term "bicyclic" as used herein intends a structure with two closed rings. As further used herein, the two rings in a bicyclic structure can be the same or different. Either of the rings in a bicyclic structure may be heterocyclic.

By the term "effective amount" of a compound as provided herein is meant a sufficient amount of the compound to provide the desired treatment or preventive effect. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease that is being treated, the particular compound used, its mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation. It is preferred that the

effective amount be essentially non-toxic to the subject, but it is contemplated that some toxicity will be acceptable in some circumstances where higher dosages are required.

By "pharmaceutically acceptable carrier" is meant a material that is not biologically or otherwise undesirable, *i.e.*, the material may be administered to an individual along with the compounds of the invention without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

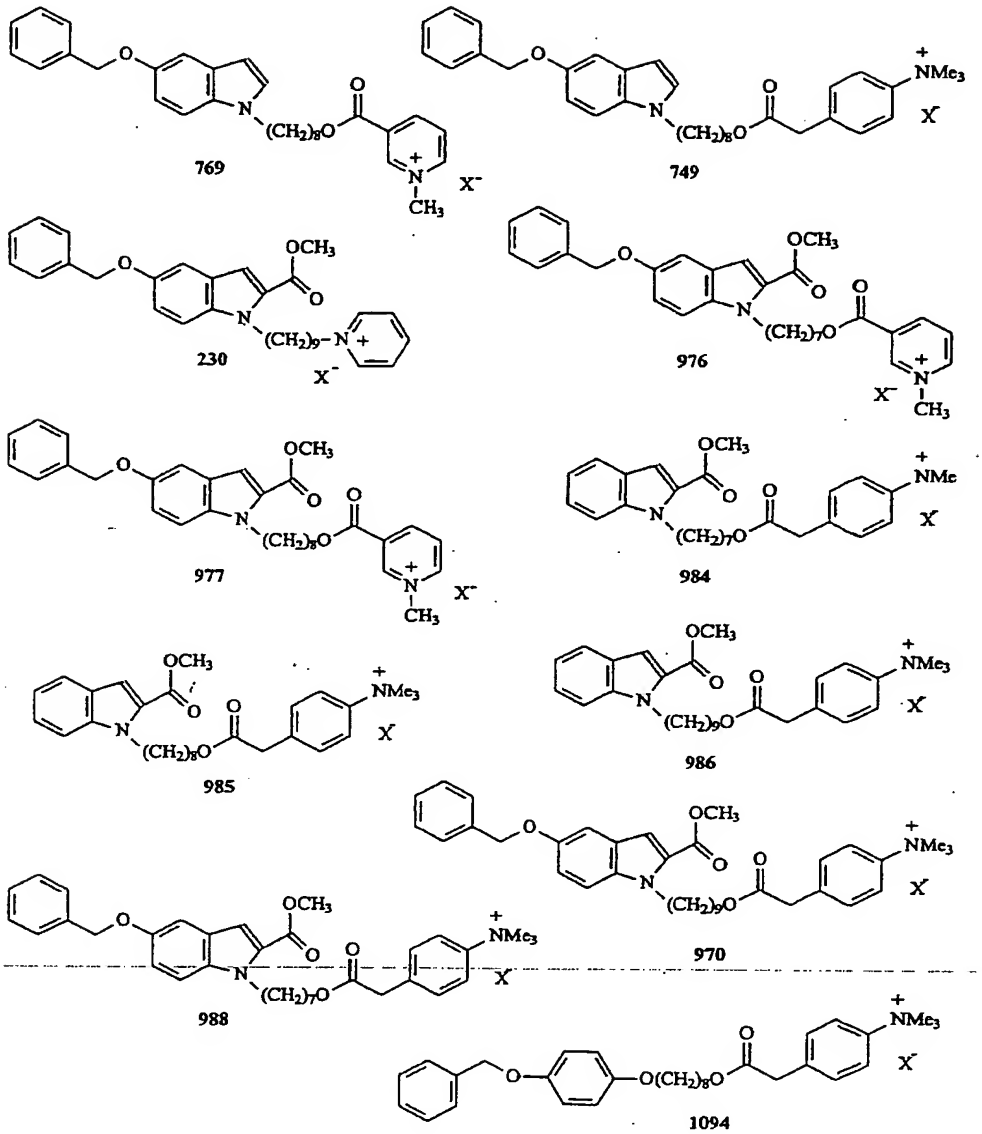
As used herein, "NAD synthetase enzyme" is defined as the enzyme that catalyzes the final reaction in the biosynthesis of NAD, namely, the transformation of NaAD into NAD. As used herein, the term "catalytic sites" are defined as those portions of the NAD synthetase enzyme that bind to substrates, and cofactors, including nicotinic acid adenine dinucleotide (NaAD), NAD, adenosine triphosphate (ATP), adenosine monophosphate (AMP), pyrophosphate, magnesium and ammonia in yeast. The term "receptor site" or "receptor subsite" relates to those portions of the yeast NAD synthetase enzyme in which the yeast NAD synthetase enzyme inhibitors disclosed herein are believed to bind. For the purposes of this disclosure, the terms "catalytic site," "receptor site" and "receptor subsite" may be used interchangeably.

In one embodiment, the invention provides administering an antifungal agent to a mammal in need of such treatment or prevention. In one embodiment, the fungal agent that causes the infection is yeast. In separate embodiments of the methods of administering, the antifungal agent comprises one or more compounds in Figure 1 below. In further separate preferred embodiments of the methods of administering, the antifungal agent comprises one or more of the compounds set forth in Figure 2 below. In still further separate embodiments, the compounds administered comprise one or more of the compounds of Structure 2, Structure 4, Structure 6, Structure 7, Structure 8, Structure 10, or Structure 12. In yet further separate embodiments of the methods of

administering, the antifungal agent comprises one or more of the compounds denoted 1 to 1106 below.

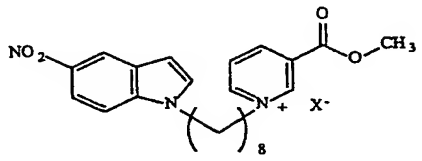
Further provided by the invention herein is preferably a method of killing yeast with an amount of yeast NAD synthetase enzyme inhibitor compound to reduce or eliminate the production of NAD whereby the yeast is killed. A method of decreasing yeast growth, comprising contacting the yeast with an amount of yeast NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby yeast growth is decreased is also provided. With respect to the method of killing yeast, as well as in the method of decreasing yeast growth, in separate embodiments of the methods the compound comprises one or more compounds of Figure 1 below. In further separate embodiments, the compound comprises one or more compounds of Figure 2 below. In a further embodiment, the compound administered is a compound of Structure 2, Structure 4, Structure 6, or Structure 7. In still further embodiments, the compounds administered comprise one or more of the compounds of Structure 8, Structure 10, or Structure 12. In yet further separate embodiments, the compounds administered comprise one or more compounds denoted 1-1106 below.

FIGURE 1: LEAD I COMPOUNDS



In yet a further embodiment, the compound comprises one or more compounds of Figure 2 below ("Lead II Compounds").

FIGURE 2: LEAD II COMPOUNDS



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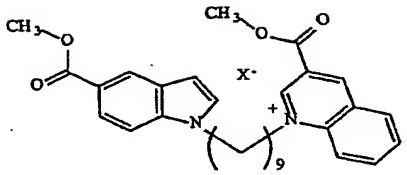

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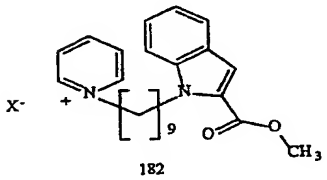

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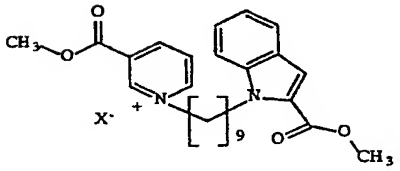

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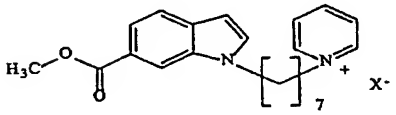

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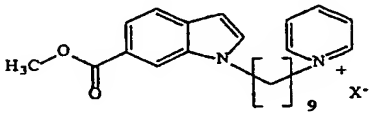

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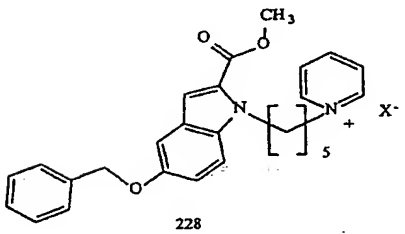

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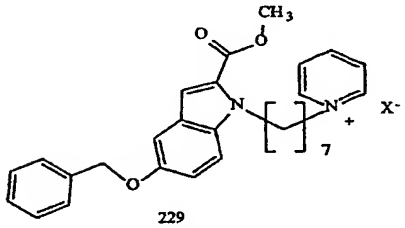

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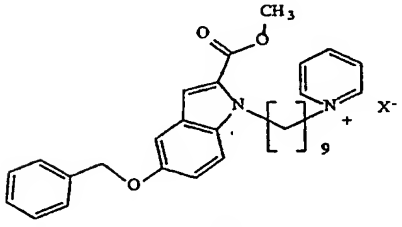

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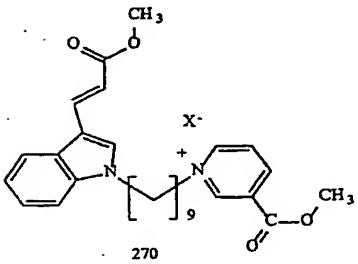

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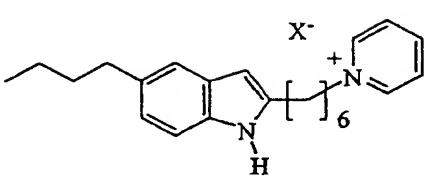

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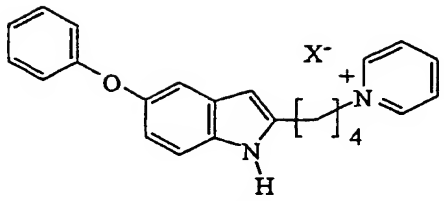

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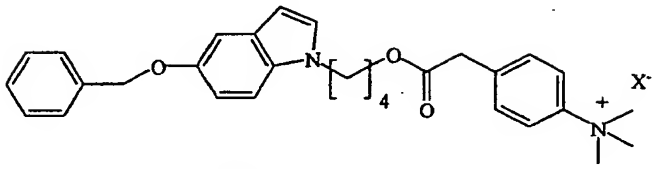

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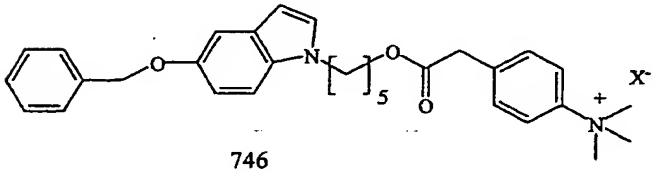

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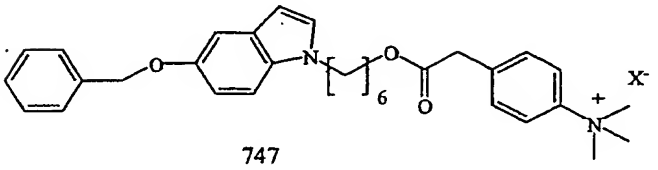

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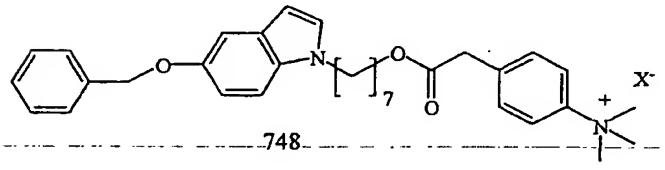

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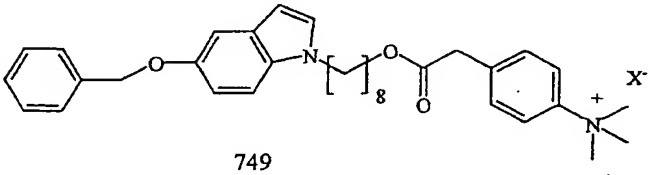

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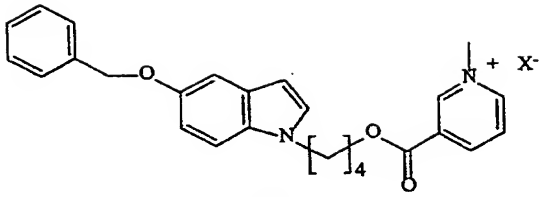

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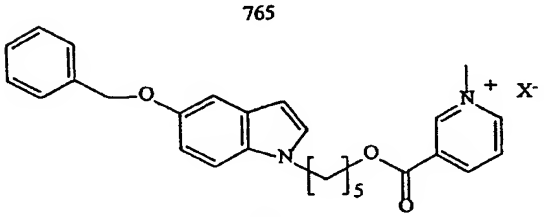

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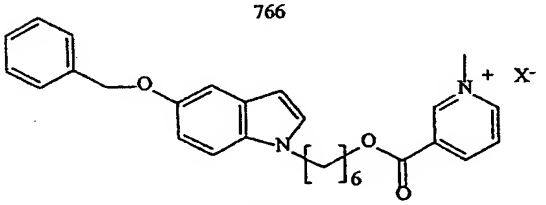

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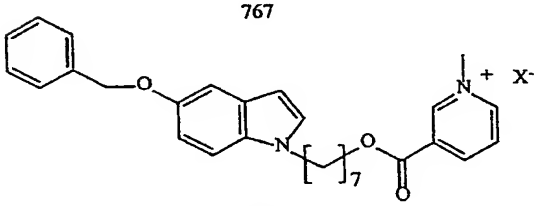

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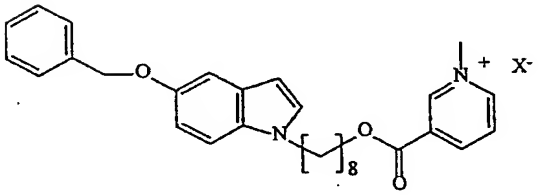

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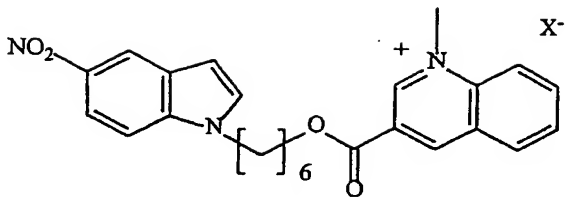

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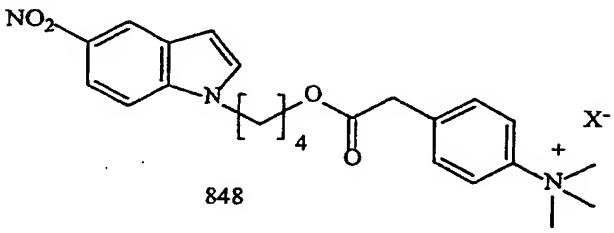

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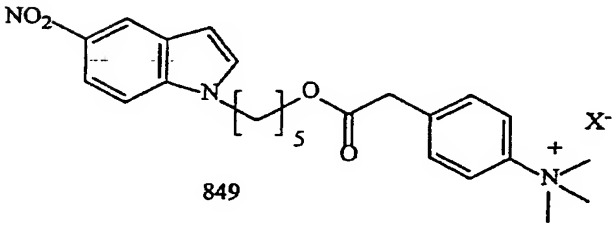

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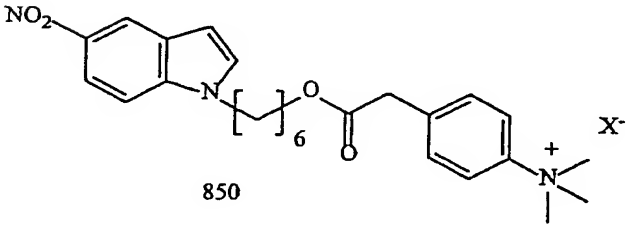

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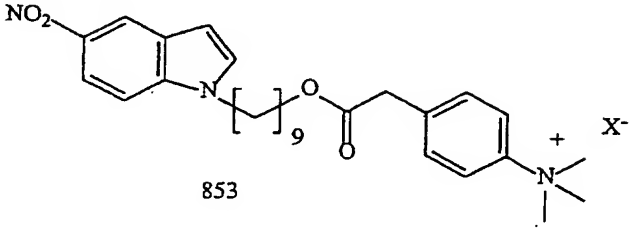

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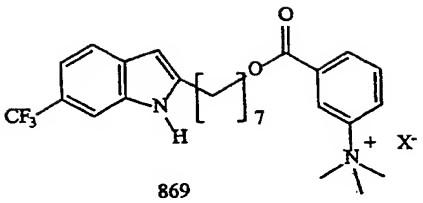

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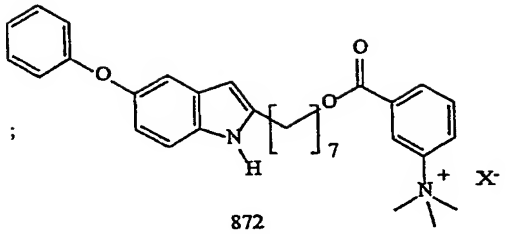

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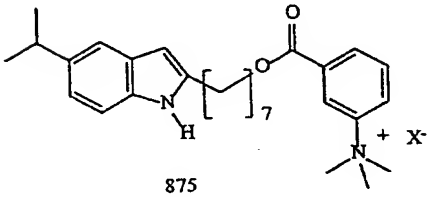

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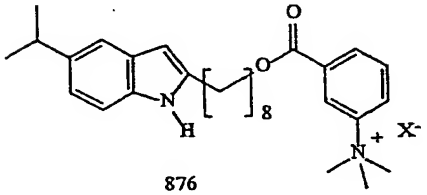

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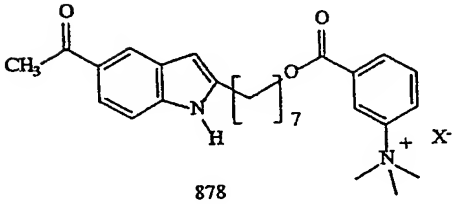

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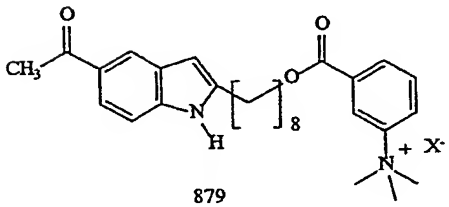

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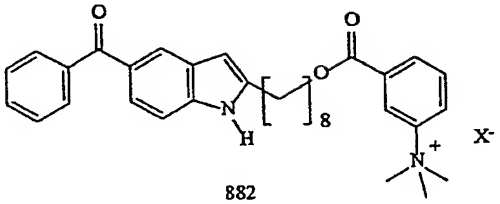

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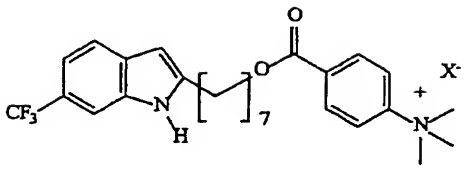

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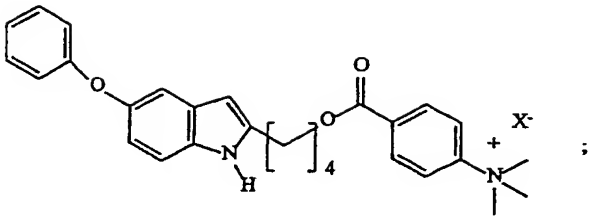

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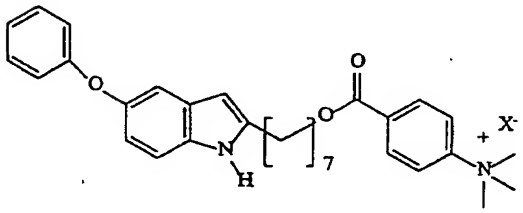

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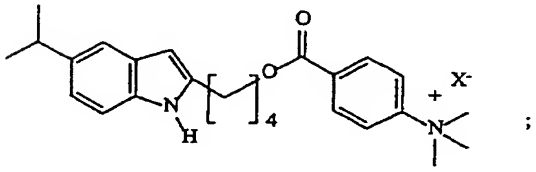

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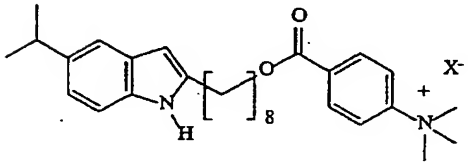

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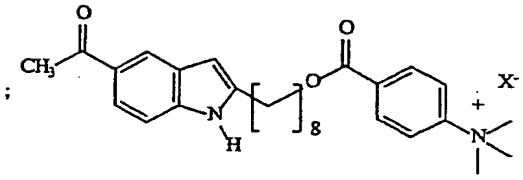

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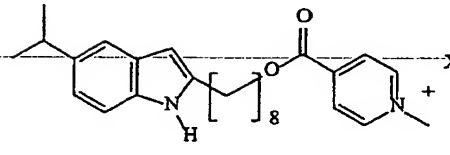

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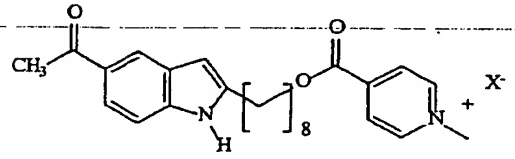

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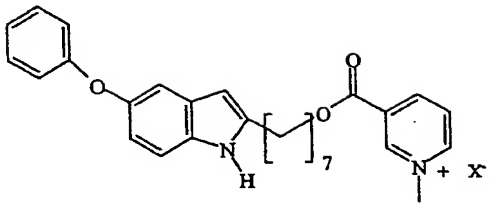

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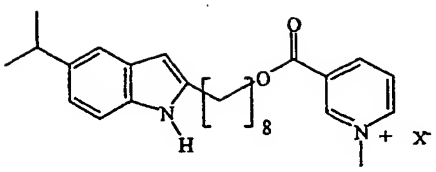

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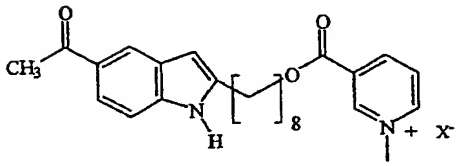

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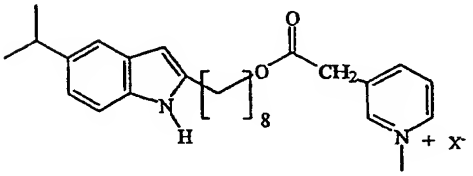

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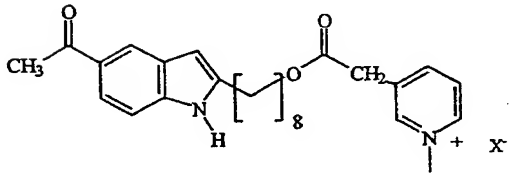

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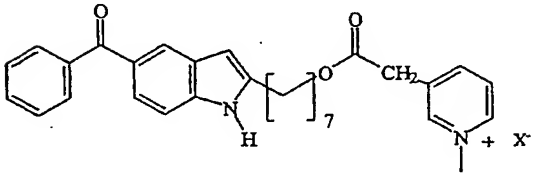

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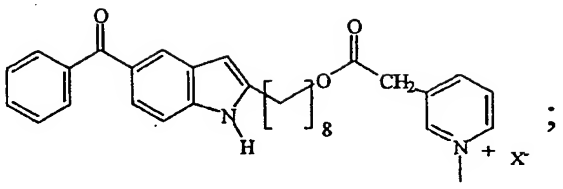

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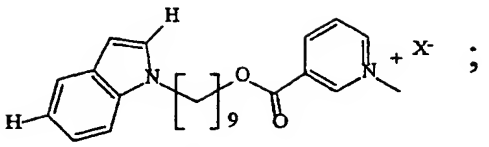

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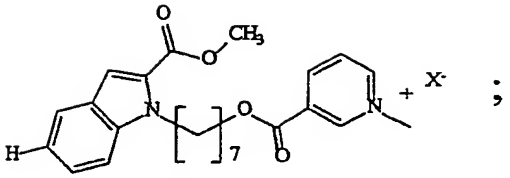

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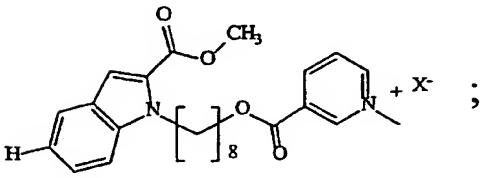

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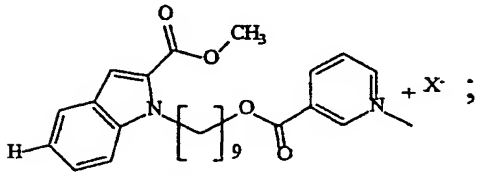

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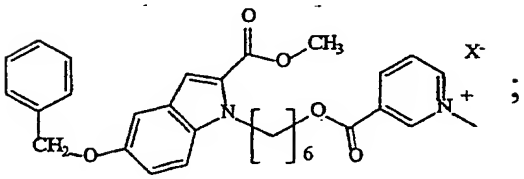

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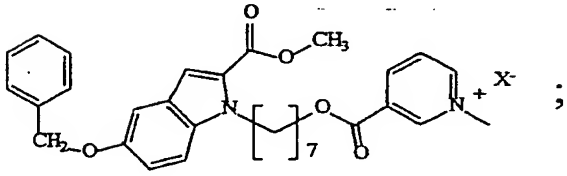

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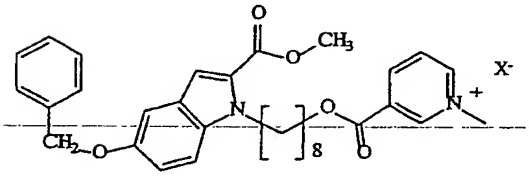

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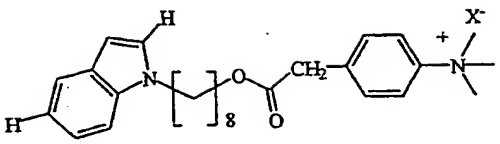

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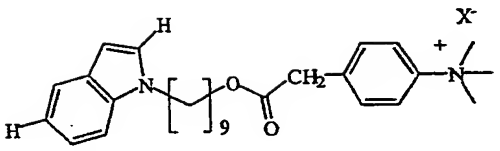

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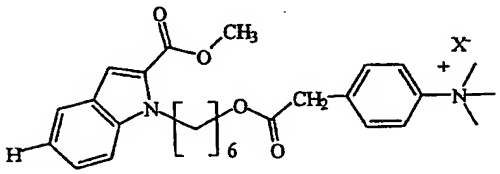

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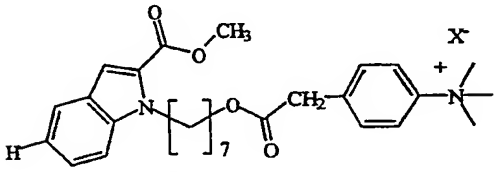

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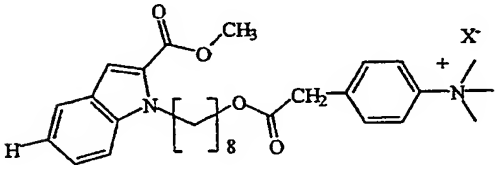

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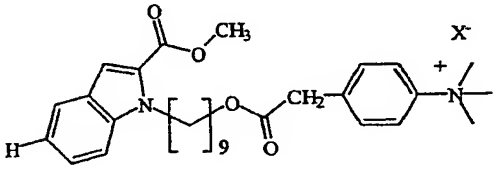

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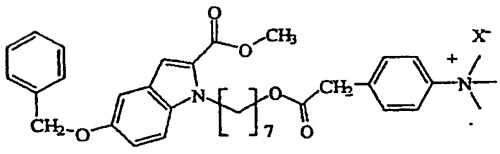

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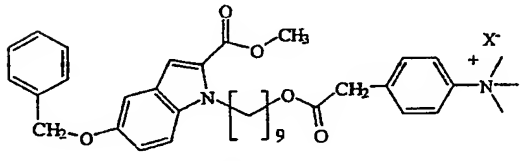

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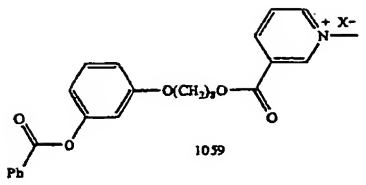

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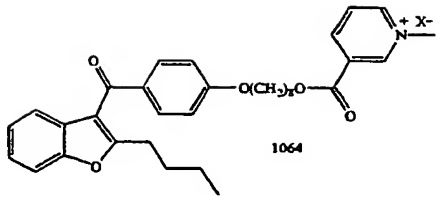

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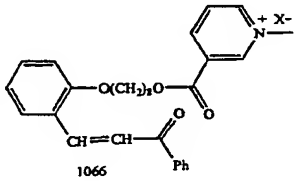

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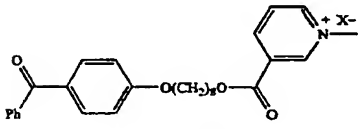

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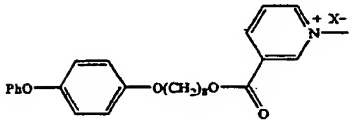

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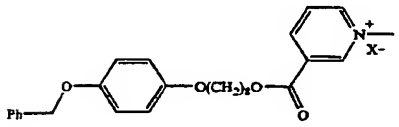

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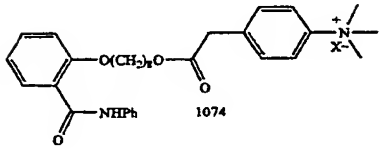

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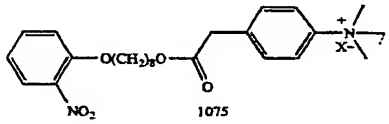

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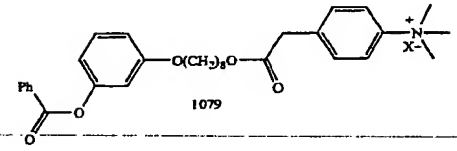

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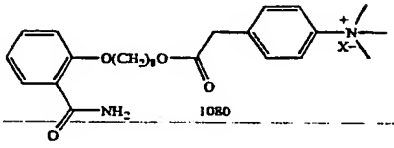

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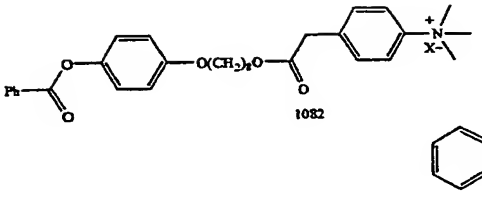

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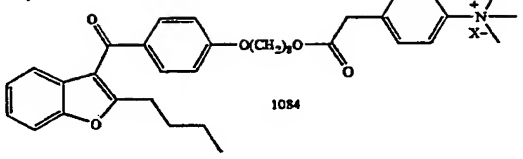

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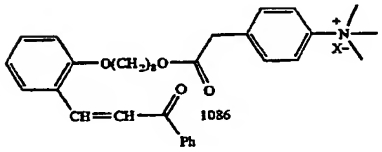

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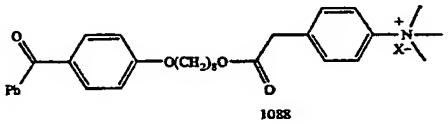

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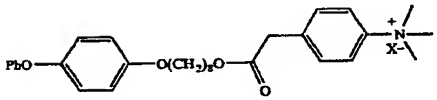

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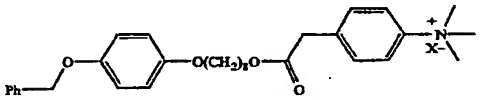

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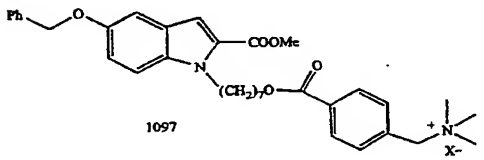

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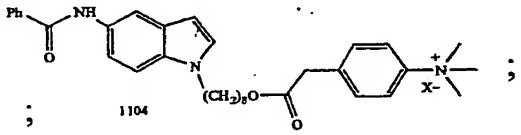

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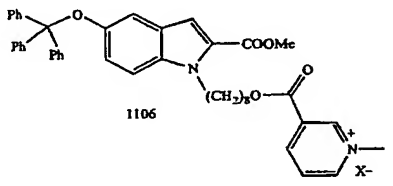
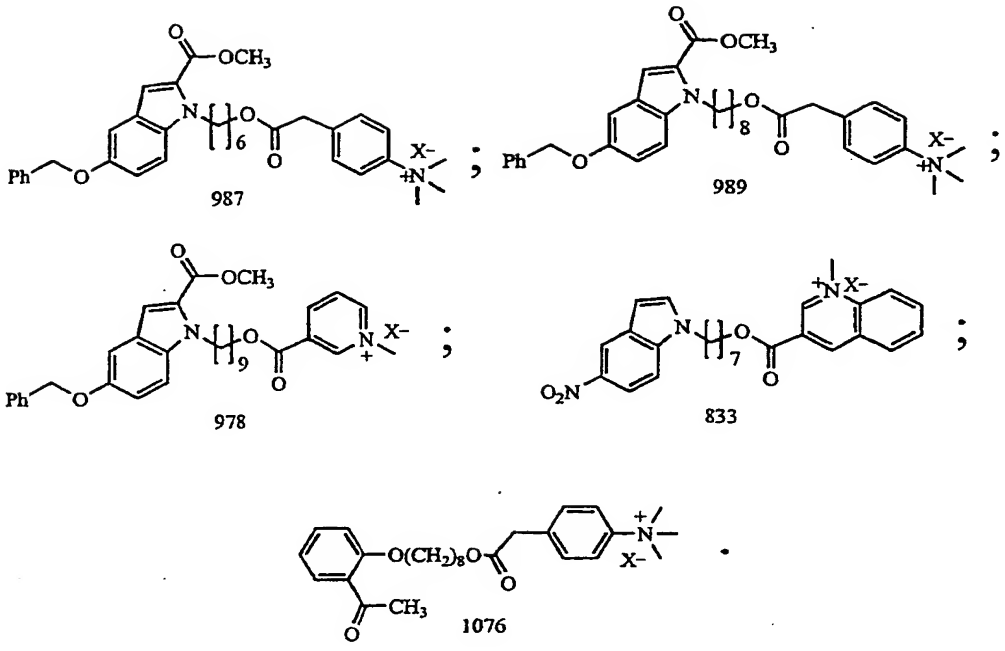


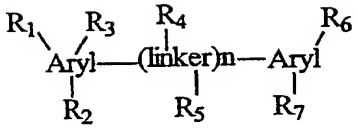
1106 .



In the above Figures 1 and 2, $X^- = F^-$, Cl^-, Br^-, I^-, acetate, or any pharmaceutically acceptable anion.

In one embodiment, the methods of the invention comprise administering a compound having the general structure of Structure 2:

STRUCTURE 2:



wherein:

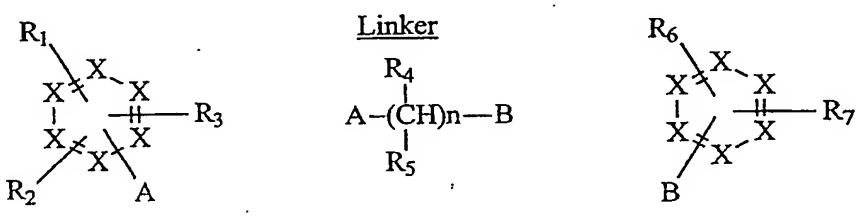
n is an integer of from 1 to 12, R_1 - R_7 each, independently, is an H, an unsubstituted or a substituted cyclic or aliphatic group, a branched or an unbranched group, and wherein the linker is a cyclic or aliphatic, branched or an unbranched alkyl, alkenyl, or an alkynyl group and wherein the linker may also contain heteroatoms. By heteroatoms, it is meant that one or more atoms is an element other than carbon.

R_1-R_7 may also be one of the following groups: an H, alkyl, alkenyl, alknyl, or an aryl. R_1-R_7, may further be a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups. Note that n may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9. The tethered active molecule, *e.g.*, in this example denoted "aryl," moieties may be the same or different.

In a further embodiment, the invention comprises administering a compound of Structure 4:

STRUCTURE 4:

DIMERS



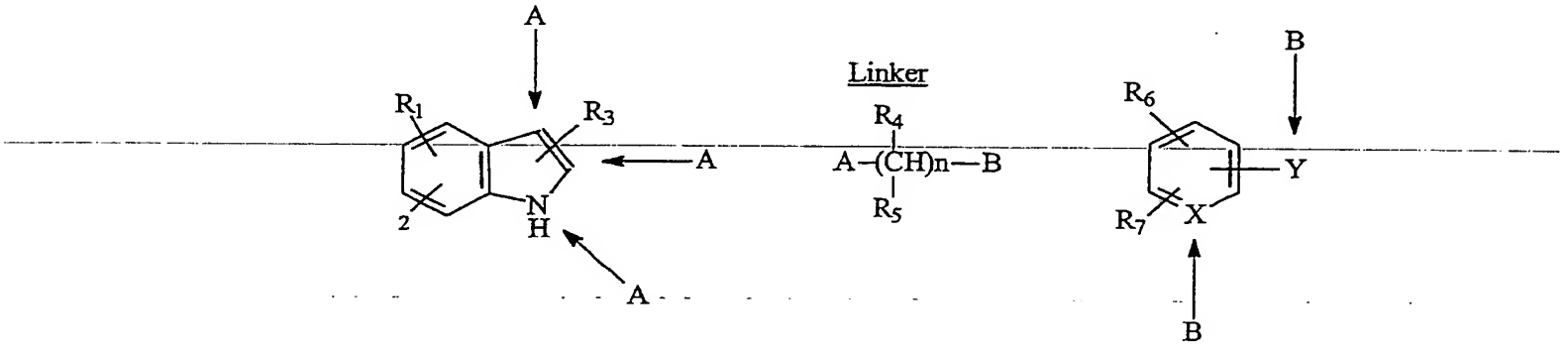
wherein:

X is a C, N, O or S within a monocyclic or bicyclic moiety, A and B represent the respective sites of attachment for the linker, n is an integer of from 1 to 12, R_1-R_7 each, independently, is an H, an unsubstituted or a substituted cyclic group, or an aliphatic group, or a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic group or an aliphatic branched or unbranched alkyl, alkenyl or alkynyl group, and wherein the linker may also contain heteroatoms.

R_1-R_7 may also be one of the following groups: an H, alkyl, alkenyl, alkynyl, or an aryl group. R_1-R_7 may also be a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups. One of skill in the art would know what moieties are considered to constitute derivatives of these groups. N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 6:

STRUCTURE 6:



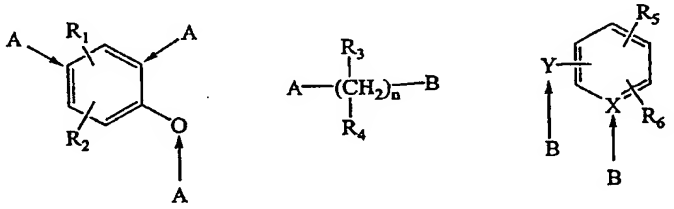
wherein:

X is C, N, O or S, Y is C, N, O, S, carboxy, ester, amide, or ketone, A and B represent the respective sites of attachment for a linker, n is an integer of from 1 to 12, and R_1-R_7 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic or aliphatic group, branched or unbranched alkyl, alkenyl, or alkynyl group and wherein the linker may also contain heteroatoms.

R_1-R_7 may also be one of the following groups: an H, alkyl, alkenyl, alknyl, or an aryl. R_1-R_7, may further be a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups. Note that n may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9. The tethered active molecule, *e.g.*, in this example denoted "aryl," moieties may be the same or different.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 7:

STRUCTURE 7



wherein:

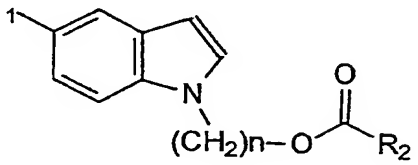
X is C, N, O or S, Y is C, N, O, S, carboxy, ester, amide, or ketone, A and B represent the respective sites of attachment for a linker, n is an integer of from 1 to 12, and R_1-R_6 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic

group, a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic or aliphatic group, branched or unbranched alkyl, alkenyl, or alkynyl group and wherein the linker may also contain heteroatoms.

R_1-R_6 may also be one of the following groups: an H, alkyl, alkenyl, or alkynyl, or an aryl group. R_1-R_6 may also be an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen and the common derivatives of these groups. One of skill in the art would know what moieties are considered to constitute derivatives of these groups. N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 8:

STRUCTURE 8:



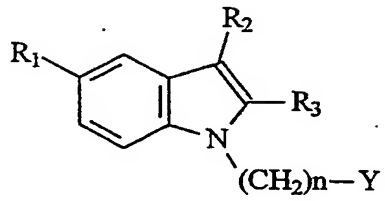
wherein:

n is an integer of from 1 to 12, R_1 is an H, methoxy, benzyloxy, or nitro and R_2 is 3-pyridyl, N-methyl-3-pyridyl, 3-quinolinyl, N-methyl-3-quinolinyl, 3-(dimethylamino)phenyl, 3-(trimethylammonio)phenyl, 4-(dimethylamino)phenyl, 4-(trimethylammonio)phenyl, 4-(dimethylamino)phenylmethyl, or 4-(trimethylammonio)phenylmethyl.

N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 10:

STRUCTURE 10:

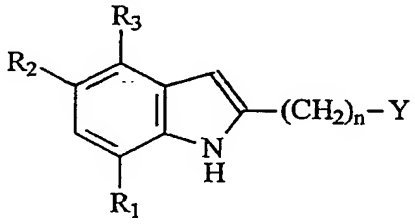


wherein:

n is an integer of from 1 to 12, R_1 is an H, CO_2H, $-OCH_3$, or $-OCH_2Ph$, R_2 is H, CO_2H, or $CH{=}CHCO_2H$, R_3 is H or CO_2H, and Y is N-linked pyridine-3-carboxylic acid, N-linked pyridine, N-linked quinoline, or N-linked isoquinoline. N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 12:

STRUCTURE 12:



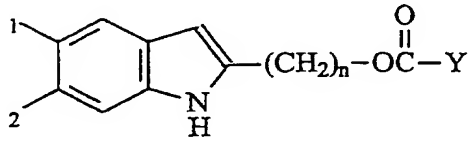
wherein:

n is an integer of from 1 to 12, R_1 is H, F, or NO_2, R_2 is H, CH_3, CF_3, NO_2, phenyl, n-

butyl, isopropyl, F, phenyloxy, triphenylmethyl, methoxycarbonyl, methoxy, carboxy, acetyl, or benzoyl, R_3 is H or CF_3 and Y is N-linked pyridine-3-carboxylic acid, N-linked pyridine, N-linked quinoline, or N-linked isoquinoline. N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In a further embodiment, the methods of the invention comprise administering a compound of Structure 14:

STRUCTURE 14:



wherein:

n is an integer of from 1 to 12, R_1 is H, phenyloxy, isopropyl, acetyl, or benzoyl, R_2 is H or CF_3, and Y is 3-(dimethylamino)phenyl, 3-(trimelthylammonio)phenyl, 4-(dimethylamino)phenyl, 4-(trimethylammonio)phenyl, 2-(phenyl)phenyl, diphenylmethyl, 3-pyridyl, 4-pyridyl, or pyridine-3-methyl. N may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

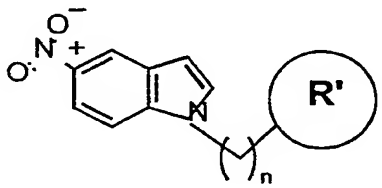
In further embodiments of the invention herein, the invention comprises administering compounds of the structures denoted in Tables 102-128 as Compounds 1-274 were synthesized utilizing the methods disclosed previously in co-pending patent application PCT/US99/00810.

For Compounds 1-274, structures denoted in Figure 6 as Fragments I-X each represent an active molecule, as defined previously herein, which can be included in the compounds of the present invention as further described in the respective Tables. In

Fragments I-X of Figure 6, the point of attachment for the linker compound is at the nitrogen.

In the chemical structures that follow, and as intended for the compounds of this invention, the symbol T^- or X^- designates generally the presence of an anion. As contemplated by the present invention, the type of anion in the compounds of this invention is not critical. The compounds of this invention may be comprised of any such moieties known generally to one of skill in the art or that follow from the synthesis methods disclosed in co-pending patent application PCT/US99/00810.

In separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to Structure 100:



Structure 100

wherein R' is as defined below in Figure 6:

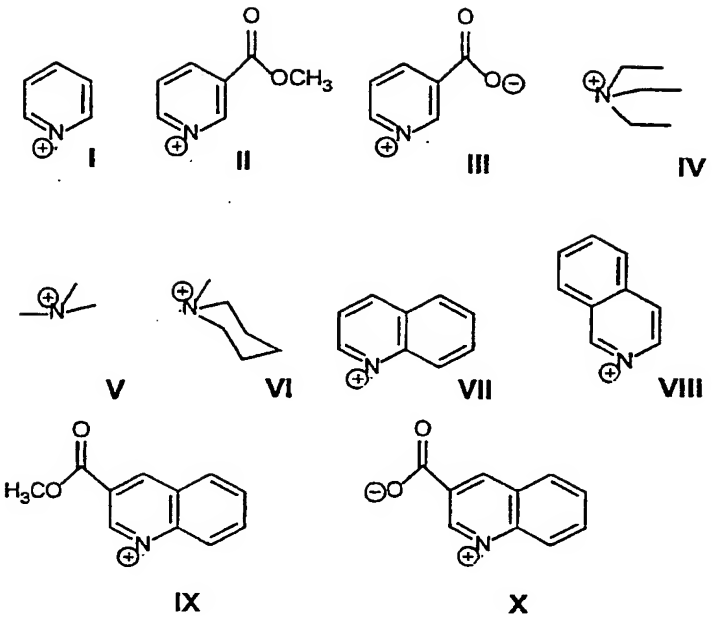


FIGURE 6

and n is an integer of from 1 to 12. N may also be from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 100 and as further defined in Table 100. For those compounds that correspond to Structure 100, n may also be an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9.

STRUCTURE 100:

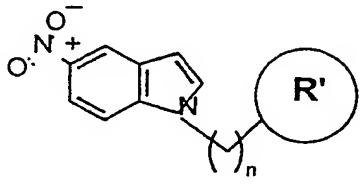


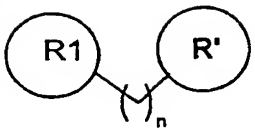
TABLE 100: SUBSTITUENT GROUPS FOR COMPOUNDS 1-24

R' n=	3	4	5	6	7	8	9
I	1	2	3	4	5	6	7
II	8	9	10	11	12	13	14
III	15	16	17	18	19	20	21
IV					22		
V					23		
VI					24		

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6 and n indicates the number of linker groups separating the two tethered active molecule groups in the compound.

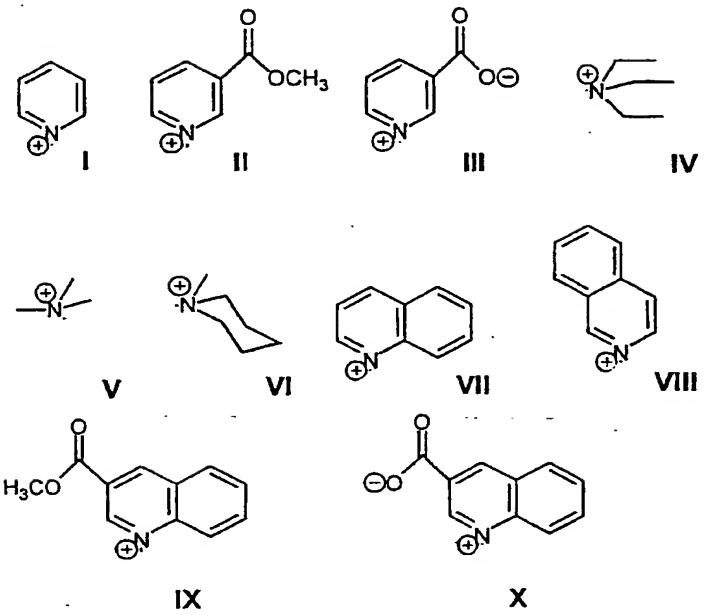
As set out below in relation to Compounds 25 – 274, Fragments A - G are set out in Figure 8. The group denoted R in A-G of Figure 8 can be a benzyl group, a methyl group or a hydrogen. The point of attachment of the linker group to Fragments A-G is at the nitrogen group.

In one embodiment, the methods of the invention comprise administering a compound corresponding to compounds of Structure 101. For those compounds that correspond to Structure 101, n is an integer of from 1 to 12, more preferably from 3 to 10, more preferably from 5 to 9 and, still more preferably from 6 to 9. The point of attachment of the linker group for both R1 and R' is at the respective nitrogen groups of each illustrated fragment.

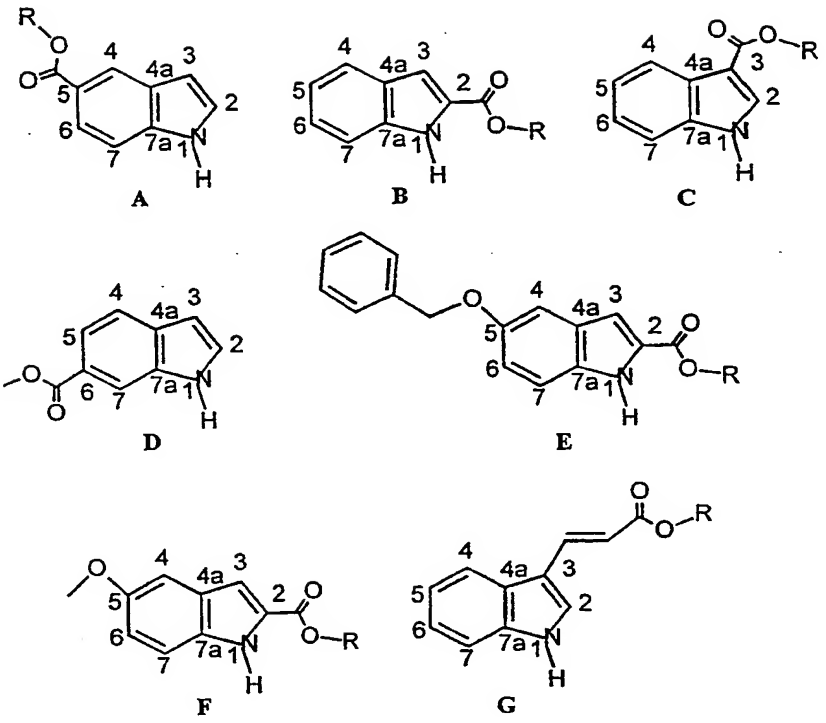


Structure 101

wherein R' is:



wherein R1 is:



wherein the R group in Fragments A-G is a benzyl group, a methyl group or a hydrogen.

In one embodiment of the invention herein, the compounds may include the Fragments illustrated below in Figure 8.

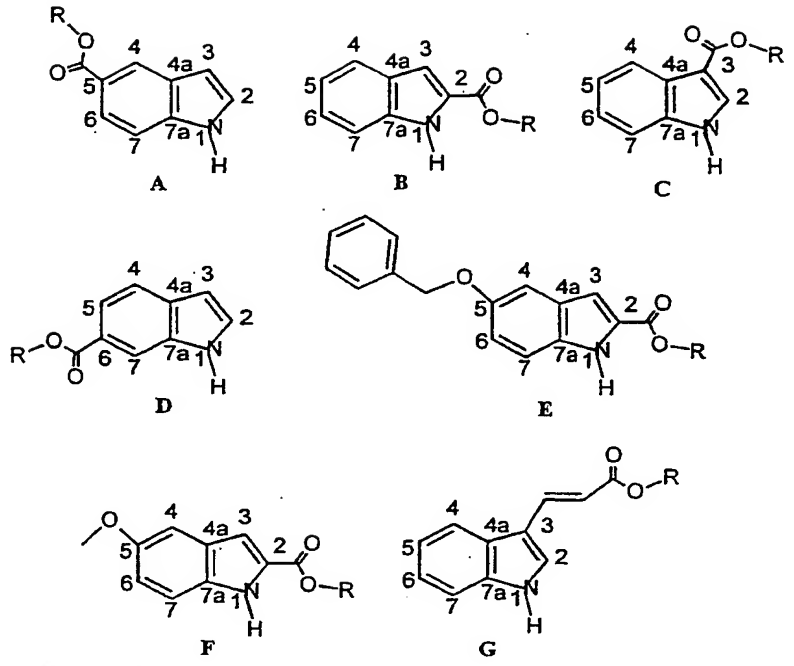


FIGURE 8: FRAGMENTS A-G IN COMPOUNDS 25-274

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 102. For those compounds that correspond to Structure 102, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 102, as further set out in Table 102.

STRUCTURE 102:

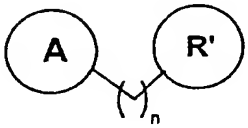


TABLE 102: SUBSTITUENT GROUPS FOR COMPOUNDS 25-48

R' n=	4	6	8
I	25	26	27
I*	28	29	30
II	31	32	33
III*	34	35	36
VII	37	38	39
VII*	40	41	42
VIII	43	44	45
VIII*	46	47	48

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, A corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and A in the respective compounds. Groups I, II, VII, VIII each have a benzyl group and Groups I*, III*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment A of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 104. For those compounds that correspond to Structure 104, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 104, as further set out in Table 104.

STRUCTURE 104:

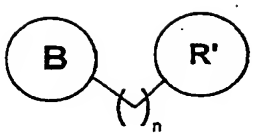


TABLE 104: SUBSTITUENT GROUPS FOR COMPOUNDS 49-66

R' n=	4	6	8
I	49	50	51
I*	52	53	54
VII	55	56	57
VII*	58	59	60
VIII	61	62	63
VIII*	64	65	66

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, B corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and B in the respective compounds. Groups I, VII, VIII each have a benzyl group and Groups I*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment B of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 106. For those compounds that correspond to Structure 106, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 106, as further set out in Table 106.

STRUCTURE 106:

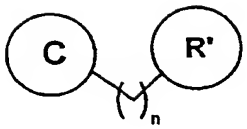


TABLE 106: SUBSTITUENT GROUPS FOR COMPOUNDS 67-90

R' n=	4	6	8
I	67	68	69
I*	70	71	72
II	73	74	75
III*	76	77	78
VII	79	80	81
VII*	82	83	84
VIII	85	86	87
VIII*	88	89	90

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, C corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and C in the respective compounds. Groups I, II, VII, VIII each have a benzyl group and Groups I*, III*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment C of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 108. For those compounds that correspond to Structure 108, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from

6 to 9. In further embodiments, the compounds herein correspond to Structure 108, as further set out in Table 108.

STRUCTURE 108:

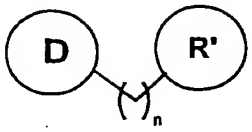


TABLE 108: SUBSTITUENT GROUPS FOR COMPOUNDS 91-108

R' n =	4	6	8
I	91	92	93
I*	94	95	96
VII	97	98	99
VII*	100	101	102
VIII	103	104	105
VIII*	106	107	108

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, D corresponds to a fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and D in the compound. Groups I, VII, VIII each have a benzyl group and Groups I*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment D of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 110. For those compounds that correspond to Structure 110, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from

6 to 9. In further embodiments, the compounds herein correspond to Structure 110, as further set out in Table 110.

STRUCTURE 110:

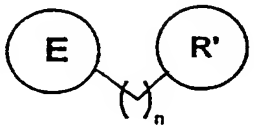


TABLE 110: SUBSTITUENT GROUPS FOR COMPOUNDS 109-126

R' n=	4	6	8
I	109	110	111
I*	112	113	114
VII	115	116	117
VII*	118	119	120
VIII	121	122	123
VIII*	124	125	126

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, E corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and E in the respective compounds. Groups I, VII, VIII each have a benzyl group and Groups I*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment E of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 112. For those compounds that correspond to Structure 112, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from

6 to 9. In further embodiments, the compounds herein correspond to Structure 112, as further set out in Table 112.

STRUCTURE 112:

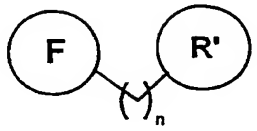


TABLE 112: SUBSTITUENT GROUPS FOR COMPOUNDS 127-144

R' n=	4	6	8
I	127	128	129
I*	130	131	132
VII	133	134	135
VII*	136	137	138
VIII	139	140	141
VIII*	142	143	144

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, F corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and F in the respective compounds. Groups I, VII, VIII each have a benzyl group and Groups I*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment F of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 114. For those compounds that correspond to Structure 114, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from

6 to 9. In further embodiments, the compounds herein correspond to Structure 114, as further set out in Table 114.

STRUCTURE 114:

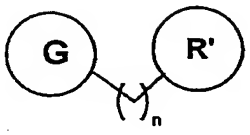


TABLE 114: SUBSTITUENT GROUPS FOR COMPOUNDS 145-162

R' n=	4	6	8
I	145	146	147
I*	148	149	150
VII	151	152	153
VII*	154	155	156
VIII	157	158	159
VIII*	160	161	162

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, G corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and G in the respective compounds. Groups I, VII, VIII each have a benzyl group and Groups I*, VII*, VIII* each have a hydrogen, respectively, in the position designated R in Fragment G of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 116. For those compounds that correspond to Structure 116, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from

6 to 9. In further embodiments, the compounds herein correspond to Structure 116, as further set out in Table 116.

STRUCTURE 116:

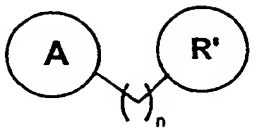


TABLE 116: SUBSTITUENT GROUPS FOR COMPOUNDS 163-178

R' n=	3	5	7	9
I	163	164	165	166
I*	167	168	169	170
II	171	172	173	174
III*	175	176	177	178

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, A corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and A in the respective compounds. Groups I, II each have a methyl group and Groups I*, III* each have a hydrogen, respectively, in the position designated R in Fragment A of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 118. For those compounds that correspond to Structure 118, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 118, as further set out in Table 118.

STRUCTURE 118:

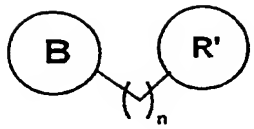


TABLE 118: SUBSTITUENT GROUPS FOR COMPOUNDS 179-194

R' n=	3	5	7	9
I	179	180	181	182
I*	183	184	185	186
II	187	188	189	190
III*	191	192	193	194

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, B corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and B in the respective compounds. Groups I, II each have a methyl group and Groups I*, III* each have a hydrogen, respectively, in the position designated R in Fragment B of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 120. For those compounds that correspond to Structure 120, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 120, as further set out in Table 120.

STRUCTURE 120:

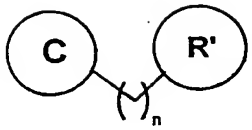


TABLE 120: SUBSTITUENT GROUPS FOR COMPOUNDS 195-210

R' n=	3	5	7	9
I	195	196	197	198
I*	199	200	201	202
II	203	204	205	206
III*	207	208	209	210

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, C corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and C in the respective compounds. Groups I, II each have a methyl group and Groups I*, II* each have a hydrogen, respectively, in the position designated R in Fragment C of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding n Structure 122. For those compounds that correspond to Structure 122, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 122, as further set out in Table 122.

STRUCTURE 122:

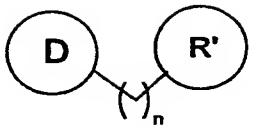


TABLE 122: SUBSTITUENT GROUPS FOR COMPOUNDS 211-226

R' n=	3	5	7	9
I	211	212	213	214
I*	215	216	217	218
II	219	220	221	222
III*	223	224	225	226

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, D corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and D in the respective compounds. Groups I, II each have a methyl group and Groups I, III each have a hydrogen, respectively, in the position designated R in Fragment D of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 124. For those compounds that correspond to Structure 124, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 124, as further set out in Table 124.

STRUCTURE 124:

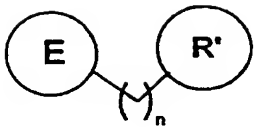


TABLE 124: SUBSTITUENT GROUPS FOR COMPOUNDS 227-242

R' n=	3	5	7	9
I	227	228	229	230
I*	231	232	233	234
II	235	236	237	238
III*	239	240	241	242

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, E corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and E in the respective compounds. Groups I, II each have a methyl group and Groups I*, III* each have a hydrogen, respectively, in the position designated R in Fragment E of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 126. For those compounds that correspond to Structure 126, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 126, as further set out in Table 126.

STRUCTURE 126:

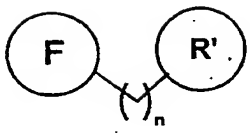


TABLE 126: SUBSTITUENT GROUPS FOR COMPOUNDS 243-258

R' n=	3	5	7	9
I	243	244	245	246
I*	247	248	249	250
II	251	252	253	254
III*	255	256	257	258

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, F corresponds to a Fragment as previously defined in Figure 8, and n indicates the number of linker groups separating Groups R' and F in the respective compounds. Groups I, II each have a methyl group and Groups I*, III* each have a hydrogen, respectively, in the position designated R in Fragment F of Figure 8.

In further separate embodiments of the invention herein, the methods of the invention comprise administering a compound corresponding to the structures set out in Structure 128. For those compounds that correspond to Structure 128, n is an integer of from 1 to 12, from 3 to 10, more preferably from 5 to 9, and still more preferably from 6 to 9. In further embodiments, the compounds herein correspond to Structure 128, as further set out in Table 128.

STRUCTURE 128:

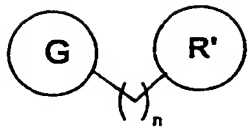


TABLE 128: SUBSTITUENT GROUPS FOR COMPOUNDS 259-274

R' n=	3	5	7	9
I	259	260	261	262
I*	263	264	265	266
II	267	268	269	270
III*	271	272	273	274

In the above Table, R' corresponds to a Fragment as previously defined in Figure 6, G corresponds to a Fragment as previously defined in Figure 6, and n indicates the number of linker groups separating Groups R' and G in the respective compounds. Groups I, II each have a methyl group and Groups I*, III* each have a hydrogen, respectively, in the position designated R in Fragment G of Figure 8.

As used herein, the following terms are defined as follows: Ph: phenyl; I-propyl= isopropyl; OPh =O-Phenyl; and diNO_2=dinitric.

In further embodiments, the compounds administered in the methods of the present invention correspond to compounds of the Structure 130 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 130 are set out in Table 130.

STRUCTURE 130:

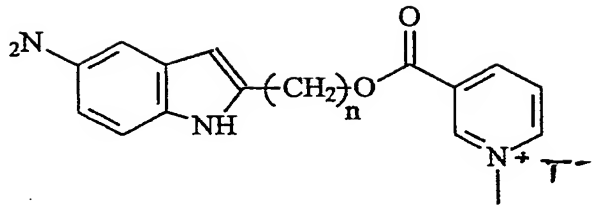


TABLE 130: COMPOUNDS CORRESPONDING TO STRUCTURE 130

n =	3	4	5	6	7	8	9
	275	276	277	278	279	280	281

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 132 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein and R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$ or 5-COOH.

Further embodiments of the compounds corresponding to Structure 132 are set out in Table 132.

STRUCTURE 132:

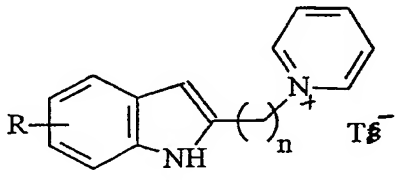


TABLE 132: COMPOUNDS 282-389 CORRESPONDING TO STRUCTURE 132

R n=	3	4	5	6	7	8
5-H	282	283	284	285	286	287
6-CF_3	288	289	290	291	292	293
5-CH_3	294	295	296	297	298	299
5,7-diF	300	301	302	303	304	305
5,7-diNO_2	306	307	308	309	310	311
5-Butyl	312	313	314	315	316	317
5-iPropyl	318	319	320	321	322	323
5-Phenyl	324	325	326	327	328	329
5-NO_2	330	331	332	333	334	335
5-Trityl	336	337	338	339	340	341
5-F	342	343	344	345	346	347
5-OPh	348	349	350	351	352	353
5-COPh	354	355	356	357	358	359
5-CF_3	360	361	362	363	364	365
5-$COCH_3$	366	367	368	369	370	371
5-OCH_3	372	373	374	375	376	377
5-$COOCH_3$	378	379	380	381	382	383
5-COOH	384	385	386	387	388	389

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 134 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$, or 5-COOH. Further embodiments of the compounds corresponding to Structure 134 are set out in Table 134.

STRUCTURE 134:

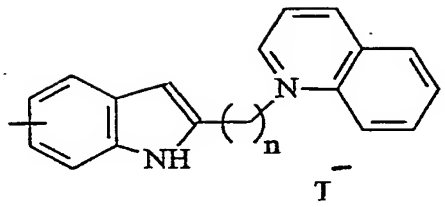


TABLE 134: COMPOUNDS 390-497 CORRESPONDING TO STRUCTURE 134

R n=	3	4	5	6	7	8
5-H	390	391	392	393	394	395
6-CF_3	396	397	398	399	400	401
5-CH_3	402	403	404	405	406	407
5,7-diF	408	409	410	411	412	413
5,7-diNO_2	414	415	416	417	418	419
5-Butyl	420	421	422	423	424	425
5-iPropyl	426	427	428	429	430	431
5-Phenyl	432	433	434	435	436	437
5-NO_2	438	439	440	441	442	443
5-Trityl	444	445	446	447	448	449
5-F	450	451	452	453	454	455
5-OPh	456	457	458	459	460	461
5-COPh	462	463	464	465	466	467
5-CF_3	468	469	470	471	472	473
5-$COCH_3$	474	475	476	477	478	479
5-OCH_3	480	481	482	483	484	485
5-$COOCH_3$	486	487	488	489	490	491
5-COOH	492	493	494	495	496	497

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 136 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$, or 5-COOH. Further embodiments of the compounds corresponding to Structure 136 are set out in Table 136.

STRUCTURE 136:

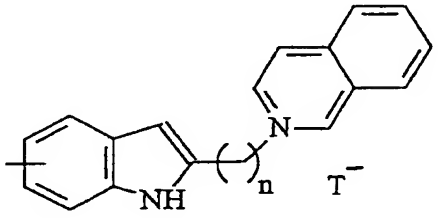


TABLE 136: COMPOUNDS 498-605 CORRESPONDING TO STRUCTURE 136

R n=	3	4	5	6	7	8
5-H	498	499	500	501	502	503
6-CF_3	504	505	506	507	508	509
5-CH_3	510	511	512	513	514	515
5,7-diF	516	517	518	519	520	521
5,7-diNO_2	522	523	524	525	526	527
5-Butyl	528	529	530	531	532	533
5-iPropyl	534	535	536	537	538	539
5-Phenyl	540	541	542	543	544	545
5-NO_2	546	547	548	549	550	551
5-Trityl	552	553	554	555	556	557
5-F	558	559	560	561	562	563
5-OPh	564	565	566	567	568	569
5-COPh	570	571	572	573	574	575
5-CF_3	576	577	578	579	580	581
5-$COCH_3$	582	583	584	585	586	587
5-OCH_3	588	589	590	591	592	593
5-$COOCH_3$	594	595	596	597	598	599
5-COOH	600	601	602	603	604	605

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 138 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 5-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh and Y is 3-N,N-dimethylaminophenyl (3-N,N-diCH_3), 4-N,N-dimethylaminophenyl (4-N,N-diCH_3), or 2-Ph. Further embodiments of the compounds corresponding to Structure 138 are set out in Table 138.

STRUCTURE 138:

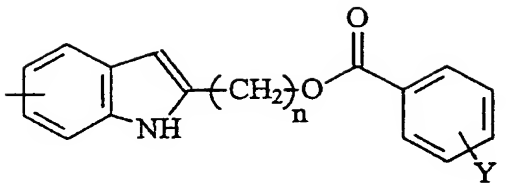


TABLE 138: COMPOUNDS 606-650 CORRESPONDING TO STRUCTURE 138

R n=	4	7	8	Y
5-CF_3	606	607	608	**3-N,N-DiCH_3**
5-CF_3	609	610	611	**4-N,N-DiCH_3**
5-CF_3	612	613	614	**2-Ph**
5-OPh	615	616	617	**3-N,N-DiCH3**
5-OPh	618	619	620	**4-N,N-DiCH_3**
5-OPh	621	622	623	**2-Ph**
5-iPropyl	624	625	626	**3-N,N-DiCH_3**
5-iPropyl	627	628	629	**4-N,N-DiCH_3**
5-iPropyl	630	631	632	**2-Ph**
5-$COCH_3$	633	634	635	**3-N,N-DiCH_3**
5-$COCH_3$	636	637	638	**4-N,N-DiCH_3**
5-$COCH_3$	639	640	641	**2-Ph**
5-COPh	642	643	644	**3-N,N-DiCH_3**
5-COPh	645	646	647	**4-N,N-DiCH_3**
5-COPh	648	649	650	**2-Ph**

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 140 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further,

from 6 to 9 and wherein R is 5-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$ or 5-COPh, and Z is $CH(Ph)_2$ or 3-Pyridyl. Further embodiments of the compounds corresponding to Structure 140 are set out in Table 140.

STRUCTURE 140:

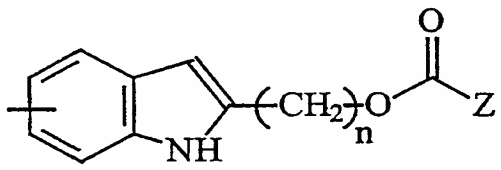


TABLE 140: COMPOUNDS 651-680 CORRESPONDING TO STRUCTURE 140

R n=	4	7	8	Z
5-CF_3	651	652	653	**$CH(Ph)_2$**
5-CF_3	654	655	656	**3-Pyridyl**
5-OPh	657	658	659	**$CH(Ph)_2$**
5-OPh	660	661	662	**3-Pyridyl**
5-iPropyl	663	664	665	**$CH(Ph)_2$**
5-iPropyl	666	667	668	**3-Pyridyl**
5-$COCH_3$	669	670	671	**$CH(Ph)_2$**
5-$COCH_3$	672	673	674	**3-Pyridyl**
5-COPh	675	676	677	**$CH(Ph)_2$**
5-COPh	678	679	680	**3-Pyridyl**

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 142 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 6-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh. Further embodiments of the compounds corresponding to Structure 142 are set out in Table 142.

STRUCTURE 142:

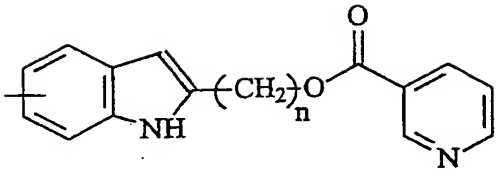


TABLE 142: COMPOUNDS 681-695 CORRESPONDING TO STRUCTURE 142

R n=	4	7	8
6-CF_3	681	682	683
5-OPh	684	685	686
5-iPropyl	687	688	689
5-$COCH_3$	690	691	692
5-COPh	693	694	695

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 144 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 6-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh. Further embodiments of the compounds corresponding to Structure 144 are set out in Table 144.

STRUCTURE 144:

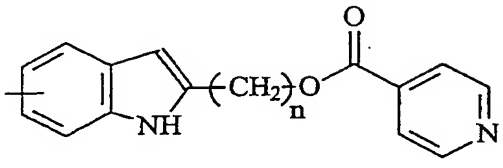


TABLE 144: COMPOUNDS 696-710 CORRESPONDING TO STRUCTURE 144

R n=	4	7	8
6-CF_3	696	697	698
5-OPh	699	700	701
5-iPropyl	702	703	704
5-$COCH_3$	705	706	707
5-COPh	708	709	710

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 146 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 146 are set out in Table 146.

STRUCTURE 146:

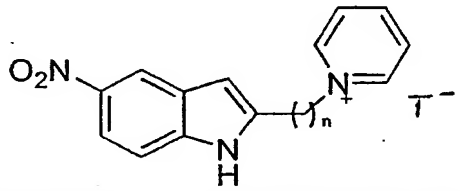


TABLE 146: COMPOUNDS 711-714 CORRESPONDING TO STRUCTURE 146

n=	3	4	5	8
	711	712	713	714

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 148, as further defined in Table 148.

STRUCTURE 148:

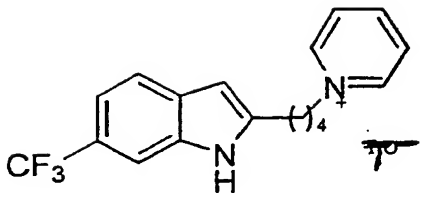


TABLE 148: COMPOUND 715 CORRESPONDING TO STRUCTURE 148

715

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 150 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 150 are set out in Table 150.

STRUCTURE 150:

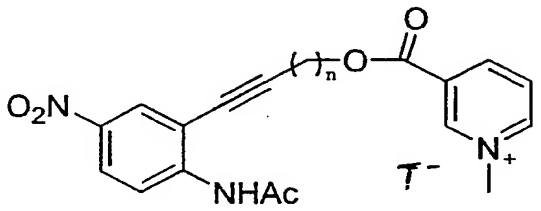


TABLE 150: COMPOUNDS 716-718 CORRESPONDING TO STRUCTURE 150

n=	2	3	4
	716	717	718

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 152 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 152 are set out in Table 152.

STRUCTURE 152:

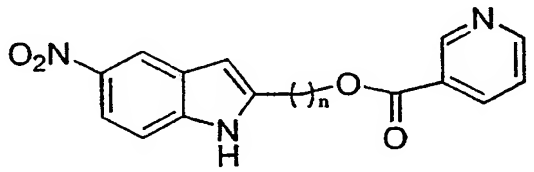


TABLE 152: COMPOUNDS 719-725 CORRESPONDING TO STRUCTURE 152

n=	3	4	5	6	7	8	9
	719	720	721	722	723	724	725

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 154 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein Z is CH(DiPh), 4-(N,N-dimethylamino)phenyl, CH_2CH_2-(3-pyridyl), or (2-phenyl)-phenyl. Further embodiments of the compounds corresponding to Structure 154 are set out in Table 154.

STRUCTURE 154:

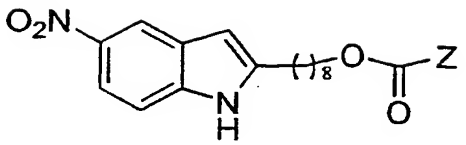


TABLE 154: COMPOUNDS 726-729 CORRESPONDING TO STRUCTURE 154

Z=	CH(DiPh)	(4-N,N-DiCH$_3$)phenyl	CH$_2$CH$_2$-(3-pyridyl)	(2-phenyl)-phenyl
	726	727	728	729

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 156 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is -OCH$_3$ or -OCH$_2$Ph. Further embodiments of the compounds corresponding to Structure 156 are set out in Table 156.

STRUCTURE 156:

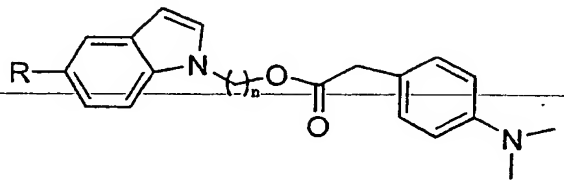


TABLE 156: COMPOUNDS 730-739 CORRESPONDING TO STRUCTURE 156

R n=	4	5	6	7	8
-OCH$_3$	730	731	732	733	734
-OCH$_2$Ph	735	736	737	738	739

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 158 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 158 are set out in Table 158.

STRUCTURE 158:

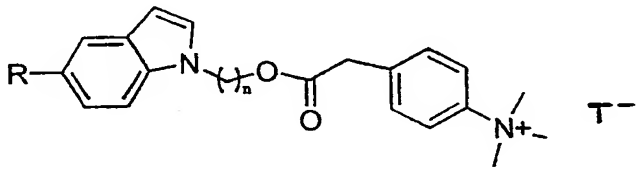


TABLE 158: COMPOUNDS 740-749 CORRESPONDING TO STRUCTURE 158

R n=	4	5	6	7	8
$-OCH_3$	740	741	742	743	744
$-OCH_2Ph$	745	746	747	748	749

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 160 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 160 are set out in Table 160.

STRUCTURE 160:

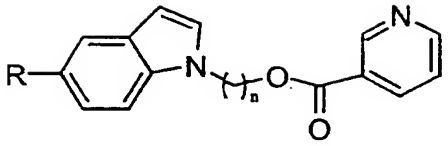


TABLE 160: COMPOUNDS 750-759 CORRESPONDING TO STRUCTURE 160

R n=	4	5	6	7	8
-OCH_3	750	751	752	753	754
-OCH_2Ph	755	756	757	758	759

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 162 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is -OCH_3 or -OCH_2Ph. Further embodiments of the compounds corresponding to Structure 162 are set out in Table 162.

STRUCTURE 162:

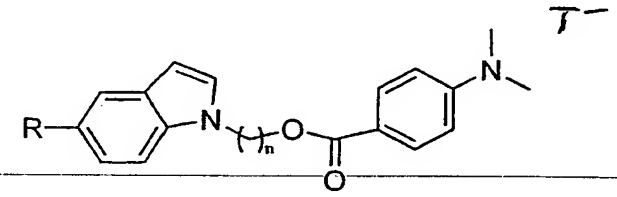


TABLE 162: COMPOUNDS 760-769 CORRESPONDING TO STRUCTURE 162

R n=	4	5	6	7	8
-OCH_3	760	761	762	763	764
-OCH_2Ph	765	766	767	768	769

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 164 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 164 are set out in Table 164.

STRUCTURE 164:

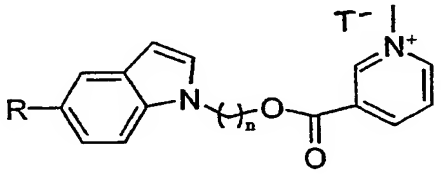


TABLE 164: COMPOUNDS 770-779 CORRESPONDING TO STRUCTURE 164

R n=	4	5	6	7	8
$-OCH_3$	770	771	772	773	774
$-OCH_2Ph$	775	776	777	778	779

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 166 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 166 are set out in Table 166.

STRUCTURE 166:

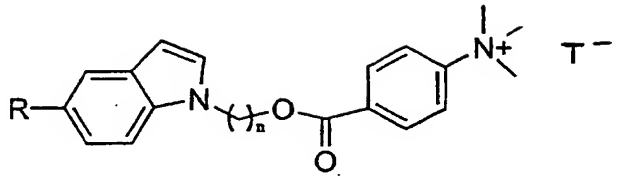


TABLE 166: COMPOUNDS 780-789 CORRESPONDING TO STRUCTURE 166

R n=	4	5	6	7	8
$-OCH_3$	780	781	782	783	784
$-OCH_2Ph$	785	786	787	788	789

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 168 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 168 are set out in Table 168.

STRUCTURE 168:

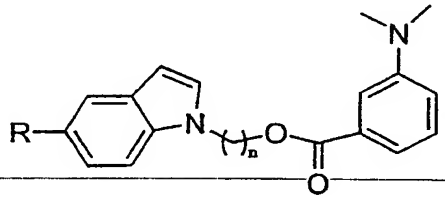


TABLE 168: COMPOUNDS 790-799 CORRESPONDING TO STRUCTURE 168

R n=	4	5	6	7	8
$-OCH_3$	790	791	792	793	794
$-OCH_2Ph$	795	796	797	798	799

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 170 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ or $-OCH_2Ph$. Further embodiments of the compounds corresponding to Structure 170 are set out in Table 170.

STRUCTURE 170:

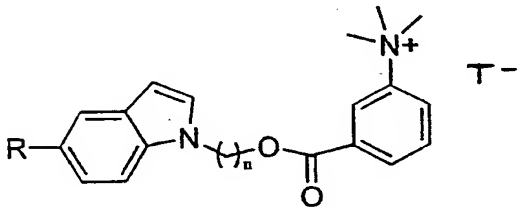


TABLE 170: COMPOUNDS 800-809 CORRESPONDING TO STRUCTURE 170

R n=	4	5	6	7	8
$-OCH_3$	800	801	802	803	804
$-OCH_2Ph$	805	806	807	808	809

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 172 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ and $-OCH_2$ Ph. Further embodiments of the compounds corresponding to Structure 172 are set out in Table 172.

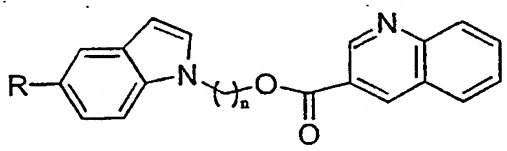


TABLE 172: COMPOUNDS 810-819 CORRESPONDING TO STRUCTURE 172

R n=	4	5	6	7	8
$-OCH_3$	810	811	812	813	814
$-OCH_2Ph$	815	816	817	818	819

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 174 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is $-OCH_3$ and $-OCH_2$ Ph. Further embodiments of the compounds corresponding to Structure 174 are set out in Table 174.

STRUCTURE 174:

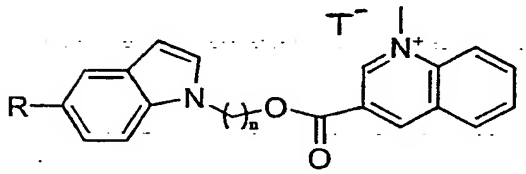


TABLE 174: COMPOUNDS 820-829 CORRESPONDING TO STRUCTURE 174

R n=	4	5	6	7	8
$-OCH_3$	820	821	822	823	824
$-OCH_2Ph$	825	826	827	828	829

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 176 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein Z is 3-quinoline, 3-(N,N-dimethylamino)phenyl, or 4-(N,N-dimethylamino)phenyl. Further embodiments of the compounds corresponding to Structure 176 are set out in Table 176.

STRUCTURE 176:

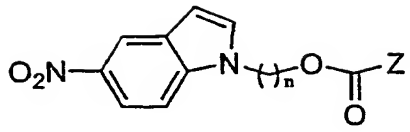


TABLE 176: COMPOUNDS 830-847 CORRESPONDING TO STRUCTURE 176

Z n=	4	5	6	7	8	9
3-quinoline	830	831	832	833	834	835
3-(N,N-diCH$_3$) phenyl	836	837	838	839	840	841
4-(N,N-diCH$_3$) phenyl	842	843	844	845	846	847

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 178 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 178 are set out in Table 178.

STRUCTURE 178:

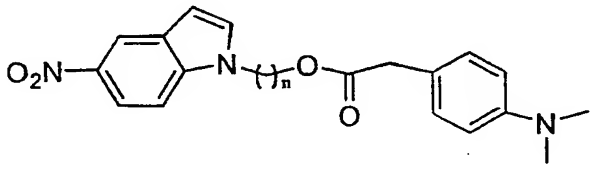


TABLE 178: COMPOUNDS 848-853 CORRESPONDING TO STRUCTURE 178

N=	4	5	6	7	8	9
	848	849	850	851	852	853

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 180 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 180 are set out in Table 180.

STRUCTURE 180:

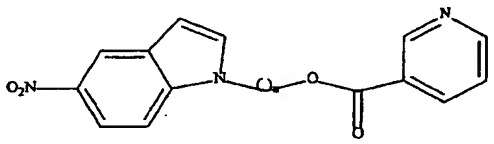


TABLE 180: COMPOUNDS 854-860 CORRESPONDING TO STRUCTURE 180

n=	2	3	4	5	6	7	8
	854	855	856	857	858	859	860

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 182 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9. Further embodiments of the compounds corresponding to Structure 182 are set out in Table 182.

STRUCTURE 182:

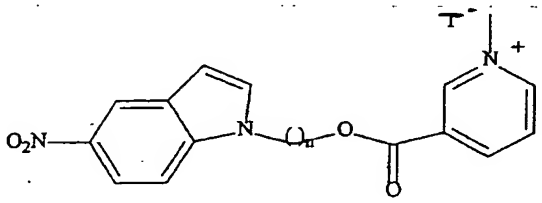


TABLE 182: COMPOUNDS 861-867 CORRESPONDING TO STRUCTURE 182

n=	2	3	4	5	6	7	8
	861	862	863	864	865	866	867

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 184 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh. Further embodiments of the compounds corresponding to Structure 184 are set out in Table 184.

STRUCTURE 184:

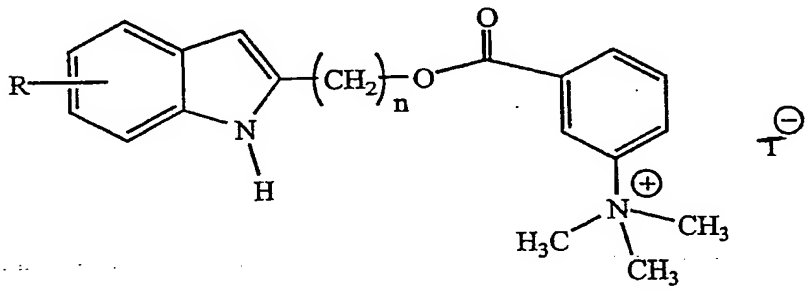


TABLE 184: COMPOUNDS 868-882 CORRESPONDING TO STRUCTURE 184

R n=	4	7	8
6-CF_3	868	869	870
5-OPh	871	872	873
5-$CH(CH_3)_2$	874	875	876
5-$COCH_3$	877	878	879
5-COPh	880	881	882

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 186 wherein n is an

integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh. Further embodiments of the compounds corresponding to Structure 186 are set out in Table 186.

STRUCTURE 186:

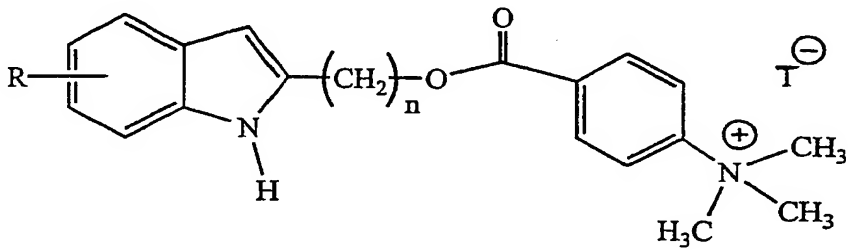


TABLE 186: COMPOUNDS 883-897 CORRESPONDING TO STRUCTURE 186

R n=	4	7	8
6-CF_3	883	884	885
5-OPh	886	887	888
5-$CH(CH_3)_2$	889	890	891
5-COCH3	892	893	894
5-COPh	895	896	897

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 188 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh. Further embodiments of the compounds corresponding to Structure 188 are set out in Table 188.

STRUCTURE 188:

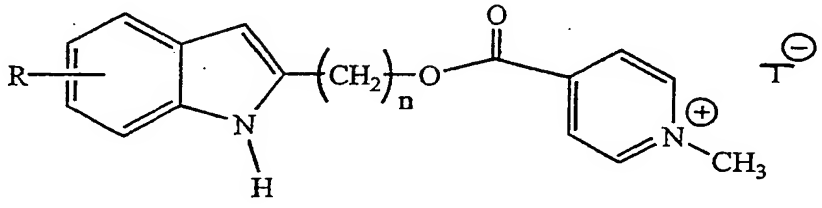


TABLE 188: COMPOUNDS 898-912 CORRESPONDING TO STRUCTURE 188

R n=	4	7	8
6-CF_3	898	899	900
5-OPh	901	902	903
5-$CH(CH_3)_2$	904	905	906
5-$COCH_3$	907	908	909
5-COPh	910	911	912

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 190 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh. Further embodiments of the compounds corresponding to Structure 190 are set out in Table 190.

STRUCTURE 190:

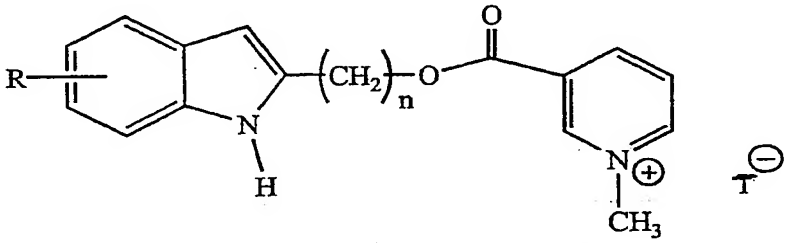


TABLE 190: COMPOUNDS 913-927 CORRESPONDING TO STRUCTURE 190

R n=	4	7	8
6-CF_3	913	914	915
5-OPh	916	917	918
5-$CH(CH_3)_2$	919	920	921
5-$COCH_3$	922	923	924
5-COPh	925	926	927

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 192 wherein n is an

integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh. Further embodiments of the compounds corresponding to Structure 192 are set out in Table 192.

STRUCTURE 192:

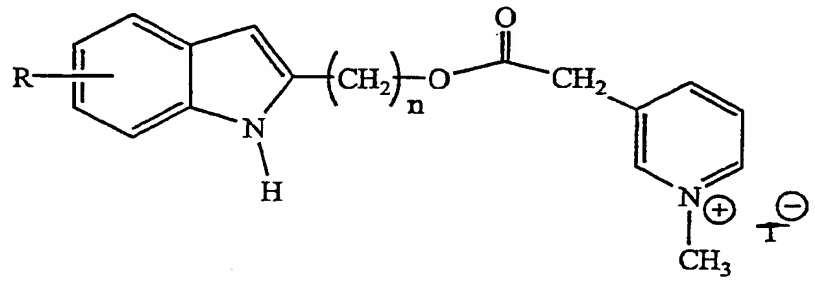


TABLE 192: COMPOUNDS 928-942 CORRESPONDING TO STRUCTURE 192

R n=	4	7	8
6-CF3	928	929	930
5-OPh	931	932	933
5-$CH(CH_3)_2$	934	935	936
5-$COCH_3$	937	938	939
5-COPh	940	941	942

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 194 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and R^1 is an H or OCH_2Ph and R^2 is H or $COOCH_3$. Further embodiments of the compounds corresponding to Structure 194 are set out in Table 194.

STRUCTURE 194:

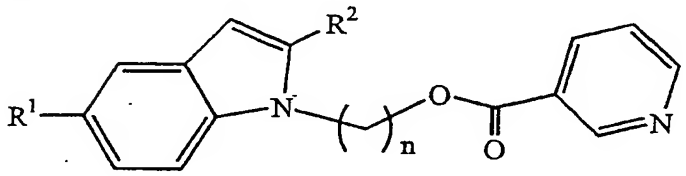


TABLE 194: COMPOUNDS 943-954 CORRESPONDING TO STRUCTURE 194

R1	R2 n=	6	7	8	9
H	H	943	944	945	946
H	$COOCH_3$	947	948	949	950
$-OCH_2Ph$	$COOCH_3$	951	952	953	954

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 196 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R^1 is an H or a $-OCH_2Ph$ and R^2 is H or $COOCH_3$. Further embodiments of the compounds corresponding to Structure 196 are set out in Table 196.

STRUCTURE 196:

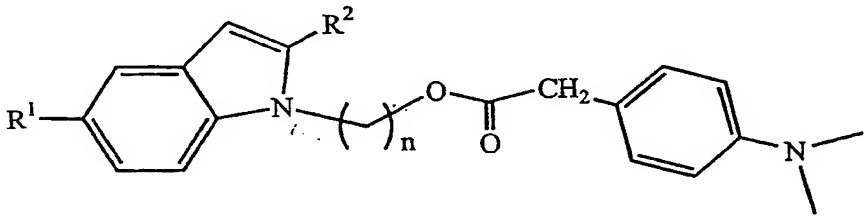


TABLE 196: COMPOUNDS 955-966 CORRESPONDING TO STRUCTURE 196

R^1	R^2 n=	6	7	8	9
H	H	955	956	957	958
H	$COOCH_3$	959	960	961	962
$-OCH_2Ph$	$COOCH_3$	963	964	965	966

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 198 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R^1 is an H or a $-OCH_2Ph$ and R^2 is H, or $COOCH_3$. Further embodiments of the compounds corresponding to Structure 198 are set out in Table 198.

STRUCTURE 198:

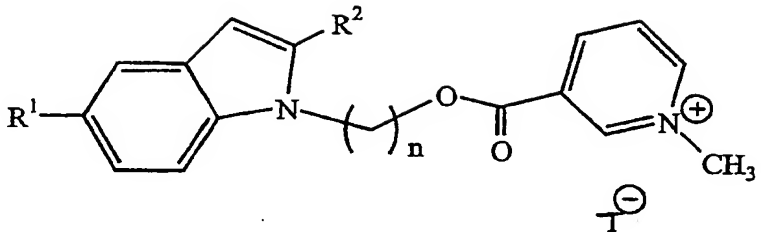


TABLE 198: COMPOUNDS 967-978 CORRESPONDING TO STRUCTURE 198

R^1	R^2 n=	6	7	8	9
H	H	967	968	969	970
H	$COOCH_3$	971	972	973	974
$-OCH_2Ph$	$COOCH_3$	975	976	977	978
$OCPh_3$	$COOCH_3$			1106	

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 200 wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R^1 is H or a $-OCH_2Ph$ and R^2 is H or $COOCH_3$. Further embodiments of the compounds corresponding to Structure 200 are set out in Table 200.

STRUCTURE 200:

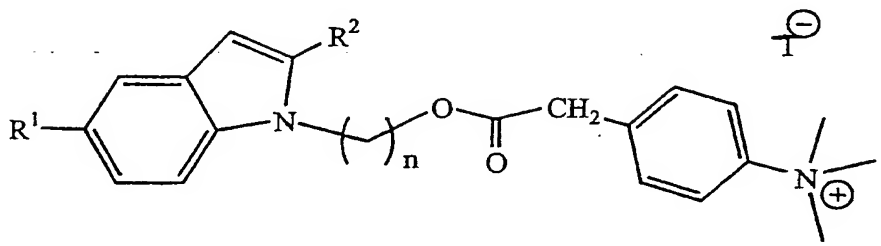
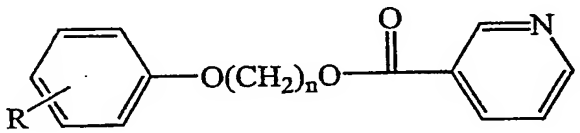


TABLE 200: COMPOUNDS 979-990 CORRESPONDING TO STRUCTURE 200

R1	R2 n=	6	7	8	9
H	H	979	980	981	982
H	$COOCH_3$	983	984	985	986
OCH2Ph	$COOCH_3$	987	988	989	990

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 202A.

STRUCTURE 202A:



In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 202A wherein n is an integer of from 1 to 12, more preferably, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is H; 4-NO_2; 2-CONHPh; 2-NO_2; 4-[1'(4'-acetylpiperazine)]; 2-$COCH_3$; 3-$OCOCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 4-[5'-(5'-phenylhydantoin)]; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 4-$CONH_2$; 3-$COCH_3$; 4-OPh; 4-(N-Phthalimide); 3-(N-Morpholine); 2-(N-pyrrolidine); 2-(N-Morpholine); or 4-OCH_2Ph. Further embodiments of the compounds corresponding to Structure 202 are set out in Table 202.

TABLE 202: COMPOUNDS 991-1021 CORRESPONDING TO STRUCTURE 202A

R=	n=4	n=7	n=8
H	991	993	
4-NO_2	992	994	995
2-CONHPh			996
2-NO_2			997
4-[1'(4'-acetylpiperazine)]			998
2-$COCH_3$			999
3-$OCOCH_3$			1000
3-OCH_3			1001
4-$COCH_3$			1002
3-OCOPh			1003
2-$CONH_2$			1004
4-CH=$CHCOCH_3$			1005
4-OCOPh			1006
4-CH=CHCOPh			1007
4-{CO-3'[2'-butylbenzo(b)furan]}			1008
3-NO_2			1009
4-[5'-(5'-phenylhydantoin)]			1010
2-CH=CHCOPh			1011
2-OCH_3			1012
4-COPh			1013
4-$CONH_2$			1014
3-$COCH_3$			1015
4-Oph			1016
4-(N-phthalimide)			1017
3-(N-morpholine)			1018
2-(N-pyrrolidine)			1019
2-(N-morpholine)			1020
4-OCH_2Ph			1021

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 204A wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 4-NO_2; 2-CONHPh; 2-NO_2; 4-[1'(4'-acetylpiperazine)]; 2-$COCH_3$; 3-$OCOCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=$CHCOCH_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 4-[5'-(5'-phenylhydantoin)];

2-CH=CHCOPh; 2-OCH_3; 4-COPh; 4-$CONH_2$; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); 3-(N-morpholine); 2-(N-pyrrolidine); 2-(N-morpholine); or 4-OCH_2Ph. Further embodiments of the compounds corresponding to Structure 204 are set out in Table 204.

STRUCTURE 204A:

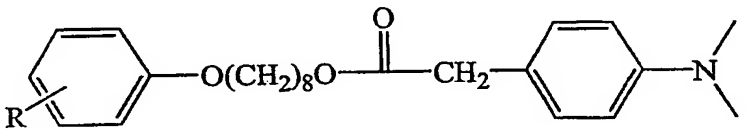


TABLE 204: COMPOUNDS 1022-1048 CORRESPONDING TO STRUCTURE 204A

R=	
4-NO_2	1022
2-CONHPh	1023
2-NO_2	1024
4-[1'(4'-acetylpiperazine)]	1025
2-$COCH_3$	1026
3-$OCOCH_3$	1027
3-OCH_3	1028
4-$COCH_3$	1029
3-OCOPh	1030
2-$CONH_2$	1031
4-CH=$CHCOCH_3$	1032
4-OCOPh	1033
4-CH=CHCOPh	1034
4-{CO-3'[2'-butylbenzo(b)furan]}	1035
3-NO_2	1036
4-[5'-(5'-phenylhydantoin)]	1037
2-CH=CHCOPh	1038
2-OCH_3	1039
4-COPh	1040
4-$CONH_2$	1041
3-$COCH_3$	1042
4-Oph	1043
4-(N-phthalimide)	1044

R=	
3-(N-morpholine)	1045
2-(N-pyrrolidine)	1046
2-(N-morpholine)	1047
4-OCH_2Ph	1048

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 206 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is H; 4-NO_2; 2-CONHPh; 2-NO_2; 2-$COCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); or 4-OCH_2Ph. Further embodiments of the compounds corresponding to Structure 206 are set out in Table 206.

STRUCTURE 206:

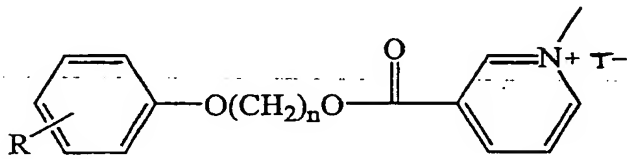


TABLE 206: COMPOUNDS 1049-1068 CORRESPONDING TO STRUCTURE 206

R=	n=4	n=7	n=8
H	1049	1051	
4-NO_2	1050	1052	1053
2-CONHPh			3054
2-NO_2			1055
2-$COCH_3$			1056
3-OCH_3			1057
4-$COCH_3$			1058
3-OCOPh			1059
2-$CONH_2$			1060
4-CH=CHCOCH$_3$			1061

4-OCOPh			1062
4-CH=CHCOPh			1063
4-{CO-3'[2'-butylbenzo(b)furan]}			1064
3-NO_2			1065
2-CH=CHCOPh			1066
2-OCH_3			1067
4-COPh			1068
3-$COCH_3$			1069
4-Oph			1070
4-(N-phthalimide)			1071
4-OCH_2Ph			1072

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 208 wherein n is an integer of from 1 to 12, from 3 to 10, from 5 to 9 and, still further, from 6 to 9 and wherein R is 4-NO_2; 2-CONHPh; 2-NO_2; 2-$COCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 3-$COCH_3$; 4-OPh; 4-(N-mhthalimide); 3-(N-morpholine); 2-(N-morpholine); or 4-OCH_2Ph. Further embodiments of the compounds corresponding to Structure 208 are set out in Table 208.

STRUCTURE 208:

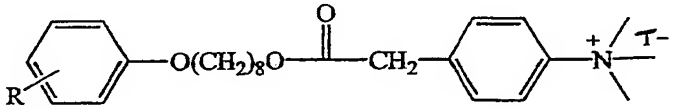


TABLE 208: COMPOUNDS 1073-1094 CORRESPONDING TO STRUCTURE 208

R=	
4-NO_2	1073
2-CONHPh	1074
2-NO_2	1075
2-$COCH_3$	1076
3-OCH_3	1077
4-$COCH_3$	1078
3-OCOPh	1079
2-$CONH_2$	1080
4-CH=$CHCOCH_3$	1081
4-OCOPh	1082
4-CH=CHCOPh	1083
4-{CO-3'[2'-butylbenzo(b)furan]}	1084
3-NO_2	1085
2-CH=CHCOPh	1086
2-OCH_3	1087
4-COPh	1088
3-$COCH_3$	1089
4-Oph	1090
4-(N-phthalimide)	1091
3-(N-morpholine)	1092
2-(N-morpholine)	1093
4-OCH_2Ph	1094

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 210 wherein R is NH_2; NMe_2; $NMe_3.I$; $NH_2.HCl$; $NMe_2.HCl$. Further embodiments of the compounds corresponding to Structure 210 are set out in Table 210.

STRUCTURE 210:

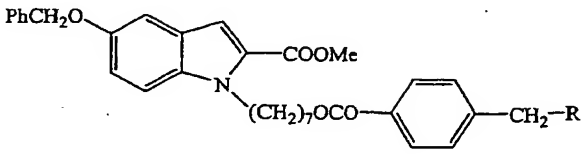


TABLE 210: COMPOUNDS 1095-1099 CORRESPONDING TO STRUCTURES 210

R=	
NH_2	1095
Nme_2	1096
$Nme_3.I$-	1097
$NH_2.HCl$	1098
$NMe_2.HCl$	1099

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 212 wherein R' is PhCONH or Ph_3C and R'' is H or $COOCH_3$. Further embodiments of the compounds corresponding to Structure 212 are set out in Table 212.

STRUCTURE 212:

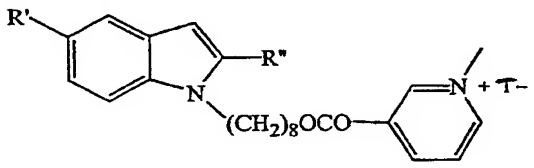


TABLE 212: COMPOUNDS 1100-1101 CORRESPONDING TO STRUCTURE 212

R'=	R''=	
PhCONH	H	1100
Ph_3C	$COOCH_3$	1101

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of the Structure 214 wherein R is 4-hydroxyphenyl or 3-hydroxy-4-methylphenyl. Further embodiments of the compounds corresponding to Structure 214 are set out in Table 214.

STRUCTURE 214:

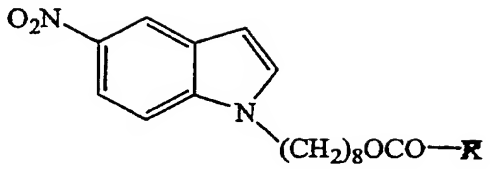


TABLE 214: COMPOUNDS 1102-1103 CORRESPONDING TO STRUCTURE 214

R=	
4-hydroxyphenyl	1102
3-hydroxy-4-methylphenyl	1103

In further embodiments, the compounds administered according to the methods of the present invention correspond to compounds of Structure 216 wherein R' is PhCONH and and R" is H or $COOCH_3$ and n= 7 or 8. Further preferred embodiments of the compounds corresponding to Structure 216 are set out in Table 216.

STRUCTURE 216:

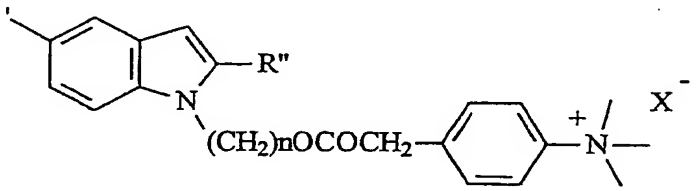
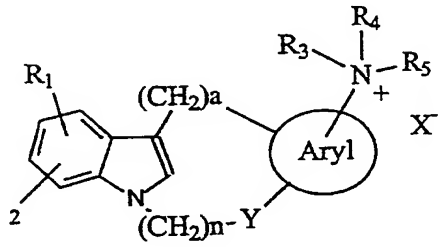


TABLE 216: COMPOUNDS 1104-1105 CORRESPONDING TO STRUCTURE 216

R'=	R"=	n=	
PhCONH	H	8	1104
$PhCH_2O$	$COOCH_3$	7	1105

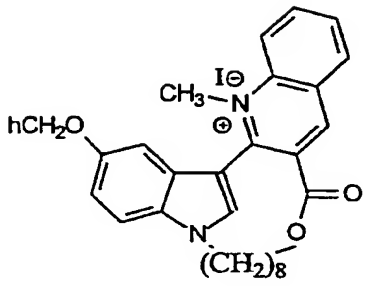
Further embodiments of the invention include compounds having Structure 300:



Structure 300

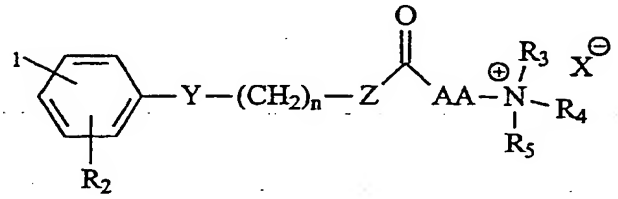
wherein Y is C, N, O, S, ester, amide, or ketone, n is an integer of from 1 to 12, a is an integer from 1-3, and R_1-R_5 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, or alkynyl, or an aryl group. R_1-R_2 may also be an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, ester, sulfonate, halogen, alkoxy, or aryloxy group. The $(CH_2)_n$ linker may be saturated or unsaturated and contain cyclic or aliphatic groups, branched or unbranched alkyl, alkenyl, or alkynyl substituents, and wherein the linker may also contain heteroatoms. The aryl group is an aromatic grouping which may contain one or more rings, and the quaternary nitrogen may be part of the ring (as, for example, in pyridines and quinolines) or outside the ring (as, for example, in anilines and aminonaphthalenes). The value for n may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

Specific examples include Structure 1300



1300

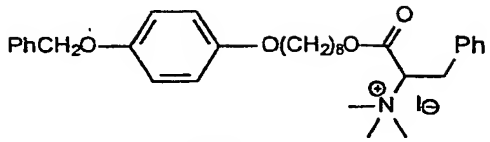
Yet another example of suitable compounds include those having Structure 400:



Structure 400

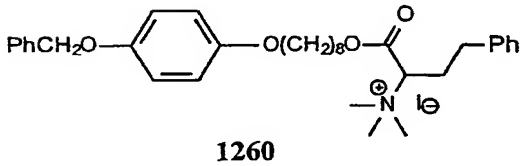
wherein Y is C, N, O, S, ester, amide, or ketone; Z is C, N, O, or S; AA is a natural or unnatural stereoisomer of an α-, β-, γ-, or δ-amino acid in which the carboxyl carbonyl is attached to Z, and the amino grouping may be a primary, secondary, tertiary, or quaternary ammonium compound; n is an integer of from 1 to 12; and R_1-R_5 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, or alkynyl, or an aryl group. R_1-R_2 may also be an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, ester, sulfonate, halogen, alkoxy, or aryloxy group. The $(CH_2)_n$ linker may be saturated or unsaturated and contain cyclic or aliphatic groups, branched or unbranched alkyl, alkenyl, or alkynyl substituents, and wherein the linker may also contain heteroatoms. The value for n may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9.

Specific examples include Structure 1230:



1230

and Structure 1260:



1260

In the method of killing yeast, as well as in the method of decreasing the growth of yeast, the NAD synthetase enzyme inhibitor is a compound that selectively binds with catalytic sites or subsites on a yeast NAD synthetase enzyme to reduce or eliminate the production of NAD by the yeast. In such methods, it is particularly preferable that there is little or no inhibitory activity on the host cell. For example, when the method is utilized to inhibit yeast activity in a mammal, it is preferred that there is little or no attendant affect on the NAD synthetase activity of the host. In one embodiment, the host is a mammal. In a further embodiment, the host is a plant.

In the methods herein, the compound is preferably administered by oral, rectal, intramuscular, intravenous, intravesicular or topical means of administration. The compounds of this invention can be administered to a cell of a subject either *in vivo* or *ex vivo*. For administration to a cell of the subject *in vivo*, as well as for administration to the subject, the compounds of this invention can be administered orally, parenterally (*e.g.*, intravenously), by intramuscular injection, by intraperitoneal injection, subcutaneous injection, transdermally, extracorporeally, topically, mucosally or the like.

Depending on the intended mode of administration, the compounds of the present invention can be in pharmaceutical compositions in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the selected composition, possibly in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

Parenteral administration of the compounds of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution of suspension in liquid prior to injection, or as emulsions. As used herein, "parenteral administration" includes intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous and intratracheal routes. One approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. *See e.g.,* U.S. Patent No. 3,610,795, which is incorporated by reference herein. These compounds can be present in a pharmaceutically acceptable carrier, which can also include a suitable adjuvant. By "pharmaceutically acceptable," it is meant a material that is not biologically or otherwise undesirable, *i.e.*, the material may be administered to an individual along with the selected compound without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained.

Routes of administration for the compounds herein are preferably in a suitable and pharmacologically acceptable formulation. When administered to a human or an animal subject, the yeast NAD synthetase enzyme inhibitor compounds of the invention herein are preferably presented to animals or humans orally, rectally, intramuscularly,

intravenously, intravesicularly or topically (including inhalation). The dosage preferably comprises between about 0.1 to about 15g per day and wherein the dosage is administered from about 1 to about 4 times per day. The preferred dosage may also comprise between 0.001 and 1 g per day, still preferably about 0.01, 0.05, 0.1, and 0.25, 0.5, 0.75 and 1.0 g per day. Further preferably, the dosage may be administered in an amount of about 1, 2.5, 5.0, 7.5,10.0, 12.5 and 15.0 g per day. The dosage may be administered at a still preferable rate of about 1, 2, 3, 4 or more times per day. Further, in some circumstances, it may be preferable to administer the compounds invention continuously, as with, for example, intravenous administration. The exact amount of the compound required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the particular compound used, its mode of administration and the like. Thus, it is not possible to specify an exact amount for every compound. However, an appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein.

If *ex vivo* methods are employed, cells or tissues can be removed and maintained outside the subject's body according to standard protocols well known in the art. The compounds of this invention can be introduced into the cells via known mechanisms for uptake of small molecules into cells (*e.g.*, phagocytosis, pulsing onto class I MHC-expressing cells, liposomes, etc.). The cells can then be infused (*e.g.*, in a pharmaceutically acceptable carrier) or transplanted back into the subject per standard methods for the cell or tissue type. Standard methods are known for transplantation or infusion of various cells into a subject.

EXAMPLES

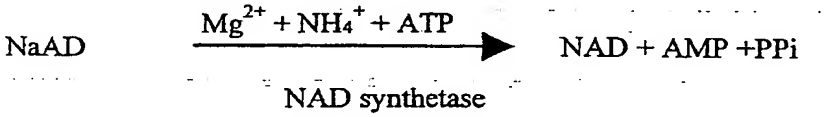
The following examples are set forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compositions and methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors

regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

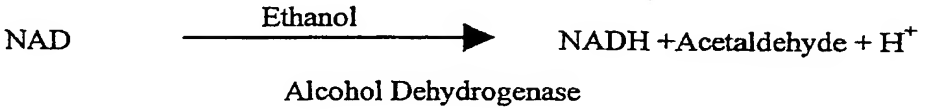
EXAMPLE 1: NAD synthetase enzyme inhibition assay- Determination of test compound concentrations providing 50% inhibition (IC_{50}) of the maximum enzyme rate.

The potential inhibitory activity of the synthetic compounds was determined by the use of a coupled enzymatic assay. The coupled assay involves two steps as summarized below.

Step 1



Step 2



The final reaction mixture includes 0.2 ml of 60 mM HEPPS buffer, pH 8.5, 10 mM $MgCl_2$, 19 mM NH_4CL_2, 20 mM KCL, 0.1mM NaAD, 0.3% n-octyl-α-D-glucopyranoside, 1% ethanol, 1 μg/ml NAD synthetase, 62.5 μg/ml yeast alcohol dehydrogenase, 0.2 mM ATP and 2.5% DMSO.

The measurement of inhibitory activities of the test compounds was facilitated by the use of a high through-put screening system (HTS system). The HTS system utilizes an integrated Sagian 2M ORCA robotic system coordinating the functions of a Beckman Biomek 2000 liquid handler and a Molecular Devices SpectraMax Plus

spectrophotometer. The 2M ORCA robotic station is responsible for the movement of all hardware and the integration of multiple stations on the worksurface. The Biomek 2000 is programmed to perform all phases of liquid dispensing and mixing. The SpectraMax Plus spectrophotometer is equipped to monitor absorbance in a 96- well plate format.

The current assay is designed for a 96-well plate format and begins with the dispensing of 0.170 mL of reaction buffer containing 60 mM HEPPS buffer, pH 8.5, 10 mM $MgCl_2$, 19 mM NH_4CL_2, 20 mM KCL, 0.118 mM NaAD, 0.3% *n*-octyl-α-D-glucopyranoside, 1.18% ethanol, 1.18 μg/ml NAD synthetase (recombinant protein from *B. subtilis*; purified), and 73.75 μg/ml yeast alcohol dehydrogenase. Once the Biomek 2000 has completed this stage of the liquid handling, a 0.005ml volume of test compound in 100% DMSO or a 0.005ml of DMSO will be dispensed in the reaction well. The Biomek 2000 mixes these components utilizing a predefined mixing program. The reaction is initiated by the addition of 0.025ml of a solution of 1.6 mM ATP dissolved in 60 mM HEPPS buffer, pH 8.5, 10 mM $MgCl_2$, 19 mM NH_4CL_2, 20 mM KCL, 2.5% DMSO, and 0.3% n-Octyl-α-D-Glucopyranoside. The reaction is monitored by measuring the increase in absorbance at 340 nm (NADH). The linear portion of the reaction is monitored for 180 sec. The initial velocity is determined using Softmax Pro, the software supplied with the Molecular Devices SpectrMax Plus spectrophotometer.

The test compounds were supplied as a stock solution with a concentration of 50mM dissolved in 100% dimethyl sulfoxide (DMSO). An initial screen was conducted on all compounds using a 2 or 3 concentration screen. The 2 panel screen used concentrations of 0.2mM and 0.1mM for the compounds. The 3 panel screen used concentrations of 0.2mM, 0.1mM, and 0.05 mM. From the initial screen, compounds which indicated the greatest inhibitory capacity were then subjected to a wider screen of concentrations (0.1mM to 0.005mM). The IC_{50} values for each compound were determined graphically from a plot of % inhibition versus rate.

Table 1. Enzyme Inhibition Data for Selected Compounds: Concentration of Test Compounds Producing 50% Inhibition (IC_{50}) of the NAD Synthetase Enzyme Rate

Compound	IC_{50} (μM)
769	20
749	25
230	12
976	20
977	10
984	20
985	15
986	10
988	10
970	20
1094	20

Example 2: Determination of minimum inhibitory concentration (MIC) against yeast.

Candida albicans (ATCC 10231), *Candida tropicalis* (ATCC 28707-amphotericin B-resistant) and *Candida tropicalis* (ATCC 750) from stock culture were subcultured on Sabouraud dextrose agar plates for 2 days at 37 °C in ambient air. At least 5 colonies from each of the cultures were inoculated into 3 mL of an approriate broth and thoroughly mixed. One-tenth mL of this suspension was transferred into 10 mL of the appropriate broth and incubated on a shaking incubator at 37 °C for 5-6 hours. Each suspension of the yeast was then adjusted with sterile saline to contain approximately $5x10^8$ CFU/mL.

Test compounds (antifungal agents) were prepared as 5 mg/mL stock solutions in 100% dimethyl sulfoxide. This was diluted 1:100 into 4 mL of diluted broth media for a starting concentration of 50 μg/mL. An additional 9 tubes were prepared with each containing 2 mL of the appropriate broth medium. Serial doubling dilutions were performed for each set of 10 tubes by transferring 2 mL of test material from the first tube to the second tube, mixing thoroughly, then transferring 2 mL to the next tube and mixing, until the tenth tube. From the tenth tube, 2 mL of mixture was discarded. Each tube is then inoculated with 0.01 mL of the yeast suspension in broth. Tubes were incubated for 37 °C for 20 hours and then scored for visible growth or no visible growth. The MIC is defined as the concentration of test compound (μg/mL) that completely inhibits growth of yeast. A positive control (without test compound in broth containing 1% DMSO inoculated with 0.01 mL of the suspension in broth) and a sterility control (only broth containing 1% DMSO) were incubated and evaluated under the same conditions. The MIC determinations and controls were performed in duplicate. The MIC values reported in Table 2 are the mean of duplicate results.

Table 2. Minimum Inhibitory Concentration (MIC) Against Yeast

Compound	*Candida albicans* (ATCC 10231) MIC (μg/mL)	*Candida tropicalis* (ATCC 28707) MIC (μg/mL)	*Candida tropicalis* (ATCC 750) MIC (μg/mL)
769	4.7	0.098	0.098
749	1.6		
230	0.78		
976	3.1		
977	1.6		
984	0.78		
985	1.6		
986	2.3		

988	0.10	0.15	0.024
970	0.8		
1094	6.2	0.78	0.78

Example 3 ***In vivo*** **toxicity: intraperitoneal (IP) dosage in mice resulting in 50% lethality (LD_{50}).**

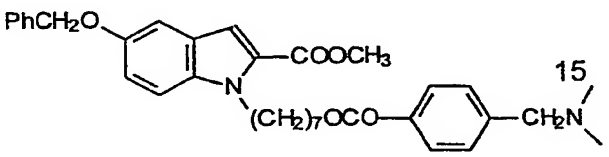
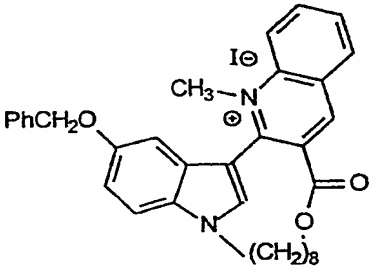
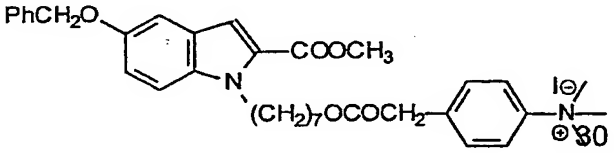
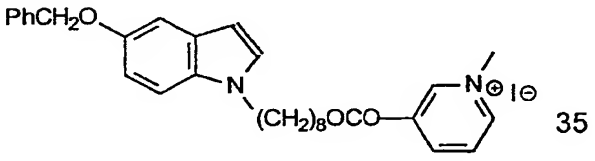
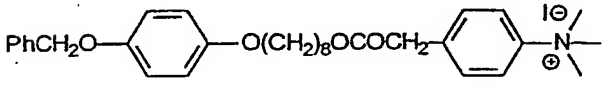
Male CD-1 mice (Charles River Labs) at age 4-6 weeks with a body weight of about 25 g were divided into groups of 5 mice each. Animals were fed with commecial diet and water *ad lib*. Each group of 5 mice received, intraperitoneally (IP), a single dosage of 0, 31.25, 62.5, 125, 250, 500, and 1,000 mg/kg compound. Test compounds were provided as 400 mg/mL stock solutions in 100% dimethyl sulfoxide (DMSO). An equivalent volume was injected into each animal. Animals were observed for 14 days following injection, and body weight was measured every other day. The LD50 was determined from a plot of death rate (%) versus log dose (mg/kg).

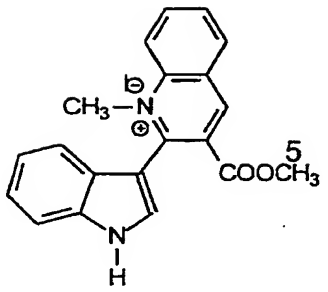
Table 3. ***In Vivo*** **Toxicity for Selected Antifungal Compounds In Mice.**

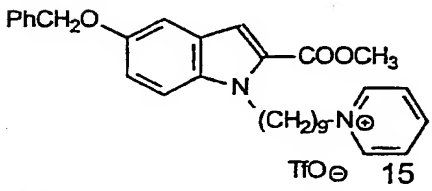
Compound	LD_{50} (mg/kg)
769	43
230	47
988	135

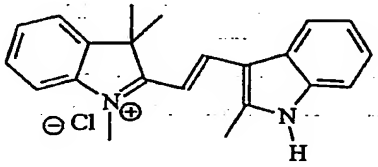
Example 4 – IN VITRO STUDY OF INHIBITION OF GROWTH AND LETHALITY AGAINST YEAST

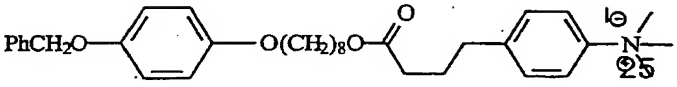
STRUCTURES OF NAD SYNTHETASE INHIBITORS USED IN THE YEAST ASSAY

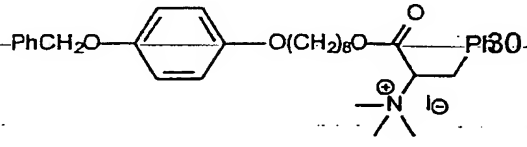
Compound	Structure	IC_{50} (μg/mL) for Inhibit. of NAD Synthetase
1096		100
1300		66
988		10
769		20
1094		20

1500  >200

230  10

1400  >200

1200 

1230  20

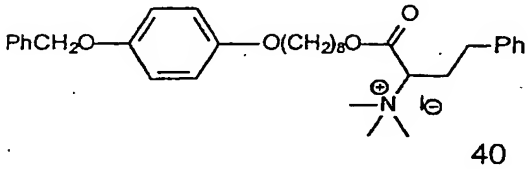
1260  30

TABLE 4A - RESULTS FOR IN VITRO STUDY OF INHIBITION OF GROWTH AND LETHALITY AGAINST YEAST

Minimum Inhibitory Conc. (MIC; μg/mL) and Minimum Lethal Conc. (MLC; μg/mL) Susceptibility Test Against Yeast Cryptococcus neoformans read at 48 and 72 hrs. All others at 24 and 48 hrs. MIC value is read at longest time.					
Comp.	**Organism**	**24 hr.**	**48 hr.**	**72 hr.**	**MLC**
769	Candida albicans	2	2		
769	Candida albicans	1	4		8
769	Candida albicans	1	2		
769	Candida albicans	1	2		8
769	Candida tropicalis	0.25	0.5		
769	Candida tropicalis	0.25	0.5		2
769	Candida tropicalis	1	1		
769	Candida tropicalis	1	1		2
769	Cryptococcus neoformans		0.5	1	
769	Cryptococcus neoformans		0.5	1	2
769	Cryptococcus neoformans		0.5	0.5	
769	Cryptococcus neoformans		1	1	2
769	Torulopsis glabrata	1	2		
769	Torulopsis glabrata	1	2		2
769	Torulopsis glabrata	0.5	1		
769	Torulopsis glabrata	0.5	1		1
230	Candida albicans	1	1		
230	Candida albicans	0.5	1		1
230	Candida albicans	1	1		
230	Candida albicans	1	1		1
230	Candida tropicalis	0.5	0.5		
230	Candida tropicalis	0.5	0.5		0.5
230	Candida tropicalis	1	1		
230	Candida tropicalis	1	1		1
230	Cryptococcus neoformans		1	1	
230	Cryptococcus neoformans		1	1	2
230	Cryptococcus neoformans		1	1	
230	Cryptococcus neoformans		1	1	2
230	Torulopsis glabrata	1	2		
230	Torulopsis glabrata	2	2		2
230	Torulopsis glabrata	1	2		

230	Torulopsis glabrata	2	2		2
988	Candida albicans	1	1		
988	Candida albicans	1	1		1
988	Candida albicans	1	2		
988	Candida albicans	1	2		2
988	Candida tropicalis	0.5	0.5		
988	Candida tropicalis	1	1		1
988	Candida tropicalis	1	1		
988	Candida tropicalis	1	1		1
988	Cryptococcus neoformans		1	1	
988	Cryptococcus neoformans		1	2	4
988	Cryptococcus neoformans		1	1	
988	Cryptococcus neoformans		1	2	4
988	Torulopsis glabrata	2	2		
988	Torulopsis glabrata	2	2		2
988	Torulopsis glabrata	1	2		
988	Torulopsis glabrata	2	2		2
1096	Candida albicans	>32	>32		
1096	Candida albicans	>32	>32		>32
1096	Candida albicans	>32	>32		
1096	Candida albicans	>32	>32		>32
1096	Candida tropicalis	4	8		
1096	Candida tropicalis	2	16		16
1096	Candida tropicalis	>32	>32		
1096	Candida tropicalis	>32	>32		>32
1096	Cryptococcus neoformans		>32	>32	
1096	Cryptococcus neoformans		8	16	>32
1096	Cryptococcus neoformans		>32	>32	
1096	Cryptococcus neoformans		32	32	>32
1096	Torulopsis glabrata	>32	>32		
1096	Torulopsis glabrata	>32	>32		>32
1096	Torulopsis glabrata	>32	>32		
1096	Torulopsis glabrata	>32	>32		>32
1094	Candida albicans	1	2		
1094	Candida albicans	1	1		4
1094	Candida albicans	2	2		
1094	Candida albicans	2	2		8
1094	Candida tropicalis	0.5	0.5		
1094	Candida tropicalis	0.5	0.5		2

1094	Candida tropicalis	1	1		
1094	Candida tropicalis	1	1		4
1094	Cryptococcus neoformans		1	1	
1094	Cryptococcus neoformans		1	1	2
1094	Cryptococcus neoformans		1	1	
1094	Cryptococcus neoformans		1	1	2
1094	Torulopsis glabrata	0.5	1		
1094	Torulopsis glabrata	1	1		4
1094	Torulopsis glabrata	0.5	1		
1094	Torulopsis glabrata	1	1		4
1300	Candida albicans	2	4		
1300	Candida albicans	2	4		8
1300	Candida albicans	4	4		
1300	Candida albicans	2	4		16
1300	Candida tropicalis	0.25	0.5		
1300	Candida tropicalis	0.5	0.5		4
1300	Candida tropicalis	2	4		
1300	Candida tropicalis	4	4		8
1300	Cryptococcus neoformans		8	8	
1300	Cryptococcus neoformans		8	8	16
1300	Cryptococcus neoformans		8	8	
1300	Cryptococcus neoformans		8	8	16
1300	Torulopsis glabrata	16	16		
1300	Torulopsis glabrata	8	16		32
1300	Torulopsis glabrata	16	16		
1300	Torulopsis glabrata	8	16		32
1230	Candida albicans	1	2		
1230	Candida albicans	1	2		2
1230	Candida albicans	2	4		
1230	Candida albicans	1	2		2
1230	Candida tropicalis	0.5	0.5		
1230	Candida tropicalis	0.5	0.5		1
1230	Candida tropicalis	1	1		
1230	Candida tropicalis	1	1		1
1230	Cryptococcus neoformans		1	1	
1230	Cryptococcus neoformans		0.5	2	4
1230	Cryptococcus neoformans		1	1	
1230	Cryptococcus neoformans		1	2	4
1230	Torulopsis glabrata	2	2		

1230	Torulopsis glabrata	2	2		2
1230	Torulopsis glabrata	1	2		
1230	Torulopsis glabrata	2	2		2
1260	Candida albicans	2	2		
1260	Candida albicans	2	2		2
1260	Candida albicans	2	2		
1260	Candida albicans	2	2		4
1260	Candida tropicalis	1	1		
1260	Candida tropicalis	1	1		1
1260	Candida tropicalis	2	2		
1260	Candida tropicalis	2	2		2
1260	Cryptococcus neoformans		1	1	
1260	Cryptococcus neoformans		1	1	2
1260	Cryptococcus neoformans		1	1	
1260	Cryptococcus neoformans		1	1	2
1260	Torulopsis glabrata	2	2		
1260	Torulopsis glabrata	2	2		2
1260	Torulopsis glabrata	2	2		
1260	Torulopsis glabrata	2	2		2
1200	Candida albicans	2	2		
1200	Candida albicans	2	2		2
1200	Candida albicans	2	2		
1200	Candida albicans	2	2		2
1200	Candida tropicalis	1	1		
1200	Candida tropicalis	1	1		1
1200	Candida tropicalis	1	1		
1200	Candida tropicalis	1	1		1
1200	Cryptococcus neoformans		2	2	
1200	Cryptococcus neoformans		2	2	4
1200	Cryptococcus neoformans		2	2	
1200	Cryptococcus neoformans		2	2	4
1200	Torulopsis glabrata	1	2		
1200	Torulopsis glabrata	1	2		2
1200	Torulopsis glabrata	1	1		
1200	Torulopsis glabrata	1	1		1
1400	Candida albicans	>32	>32		
1400	Candida albicans	>32	>32		>32
1400	Candida albicans	>32	>32		
1400	Candida albicans	>32	>32		>32

1400	Candida tropicalis	16	32		
1400	Candida tropicalis	16	16		16
1400	Candida tropicalis	>32	>32		
1400	Candida tropicalis	>32	>32		>32
1400	Cryptococcus neoformans		>32	>32	
1400	Cryptococcus neoformans		>32	>32	>32
1400	Cryptococcus neoformans		>32	>32	
1400	Cryptococcus neoformans		>32	>32	>32
1400	Torulopsis glabrata	>34	>32		
1400	Torulopsis glabrata	>32	>32		>32
1400	Torulopsis glabrata	>33	>32		
1400	Torulopsis glabrata	>32	>32		>32
1500	Candida albicans	32	>32		
1500	Candida albicans	>32	>32		>32
1500	Candida albicans	32	>32		
1500	Candida albicans	>32	>32		>32
1500	Candida tropicalis	4	8		
1500	Candida tropicalis	4	8		8
1500	Candida tropicalis	32	>32		
1500	Candida tropicalis	>32	>32		>32
1500	Cryptococcus neoformans		32	32	
1500	Cryptococcus neoformans		32	>32	>32
1500	Cryptococcus neoformans		32	32	
1500	Cryptococcus neoformans		32	>32	>32
1500	Torulopsis glabrata	32	>32		
1500	Torulopsis glabrata	>32	>32		>32
1500	Torulopsis glabrata	32	>32		
1500	Torulopsis glabrata	>32	>32		>32
Amphotericin B	Candida albicans	0.5	1		
Amphotericin B	Candida albicans	0.5	1		
Amphotericin B	Candida albicans	0.5	0.5		
Amphotericin B	Candida albicans	0.5	0.5		
Amphotericin B	Candida tropicalis	2	4		
Amphotericin B	Candida tropicalis	2	4		
Amphotericin B	Candida tropicalis	0.5	0.5		
Amphotericin B	Candida tropicalis	0.5	1		
Amphotericin B	Cryptococcus neoformans		0.25	0.25	
Amphotericin B	Cryptococcus neoformans		0.25	0.25	
Amphotericin B	Cryptococcus neoformans		0.5	0.5	

Amphotericin B	Cryptococcus neoformans		0.25	0.25
Amphotericin B	Torulopsis glabrata	0.5	1	
Amphotericin B	Torulopsis glabrata	0.5	1	
Amphotericin B	Torulopsis glabrata	0.5	1	
Amphotericin B	Torulopsis glabrata	0.5	0.5	
Fluconazole	Candida albicans	0.5	1	
Fluconazole	Candida albicans	0.5	2	
Fluconazole	Candida albicans	0.5	>64	
Fluconazole	Candida albicans	>64	>64	
Fluconazole	Candida tropicalis	64	>64	
Fluconazole	Candida tropicalis	>64	>64	
Fluconazole	Candida tropicalis	1	4	
Fluconazole	Candida tropicalis	1	4	
Fluconazole	Cryptococcus neoformans		>64	>64
Fluconazole	Cryptococcus neoformans		64	64
Fluconazole	Cryptococcus neoformans		4	4
Fluconazole	Cryptococcus neoformans		4	4
Fluconazole	Torulopsis glabrata	64	>64	
Fluconazole	Torulopsis glabrata	>64	>64	
Fluconazole	Torulopsis glabrata	2	8	
Fluconazole	Torulopsis glabrata	2	4	

TABLE 4B - Summary Of Minimum Lethal Concentration (MLC; μg/mL)

Plate	Compound	A	B	C	D	E	F	G	H
1	1108	4	2	4	8	4	4	2	2
2	1174	8	4	8	16	32	32	16	16
3	1072	>32	16	>32	>32	>32	>32	>32	>32
4	1127	>32	>32	>32	>32	>32	>32	>32	>32
5	0270	2	2	8	8	1	2	2	2
6	1198	2	1	2	4	2	2	2	2
7	1264	1	1	2	2	1	2	4	4
8	1274	>32	16	>32	>32	>32	>32	>32	>32
9	1308	>32	8	>32	>32	>32	>32	>32	>32
10	0951	1	1	1	2	2	2	4	4
11	0409	1	0.5	1	1	2	2	2	2
12	1197	1	1	2	2	2	2	4	4

	ISOLATE	ORGANISM
A	ATCC 750	Candida tropicalis
B	ATCC 28707	Candida tropicalis
C	KJP-000531594	Candida albicans
D	LH-000664533	Candida albicans
E	JHC-BC9951635	Torulopsis glabrata
F	ERH-BC9938274	Torulopsis glabrata
G	DLB-1027594CNC	Cryptococcus neoformans
H	SLP-BC0012854	Cryptococcus neoformans

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected without departing from the scope and spirit of the invention.

Throughout this application, where publications are referenced, the disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

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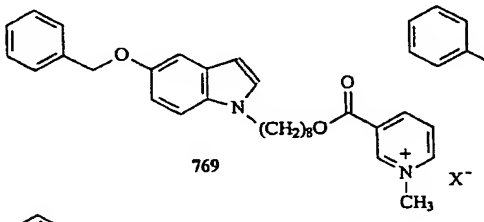
WHAT IS CLAIMED IS:

1. A method of treating or preventing an antifungal infection in a host comprising administering to a host a treatment effective or treatment preventive amount of a yeast NAD synthetase enzyme inhibitor compound.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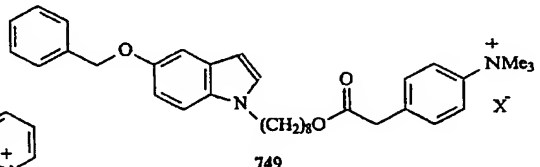
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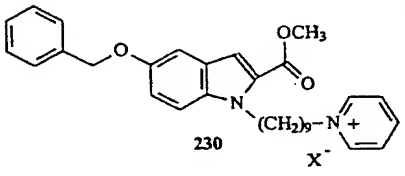
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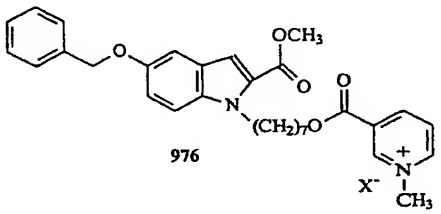
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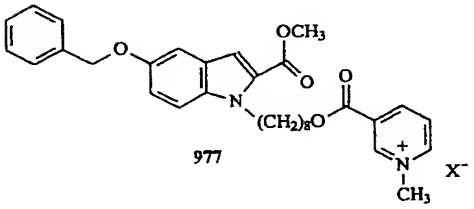
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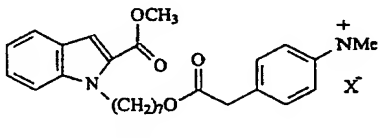
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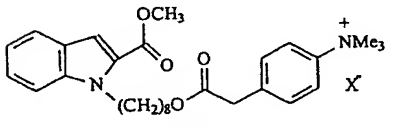
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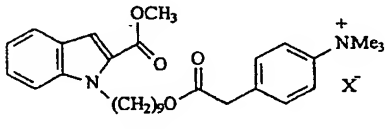
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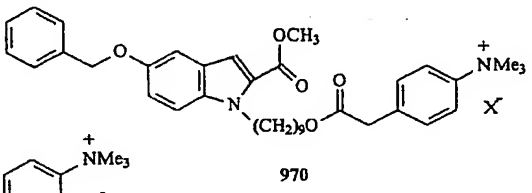
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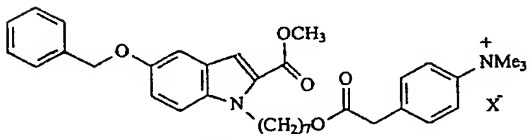
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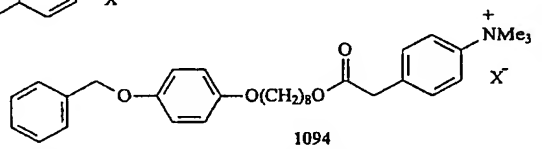
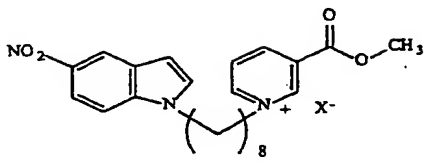

1094

2. The method of Claim 1 wherein the compound administered is selected from the group consisting of:

3. The method of Claim 1 wherein the compound administered is selected from the



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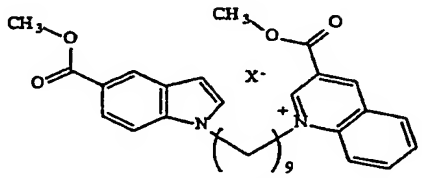

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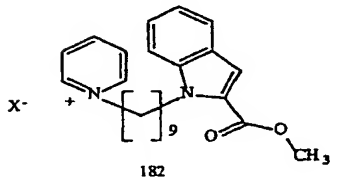

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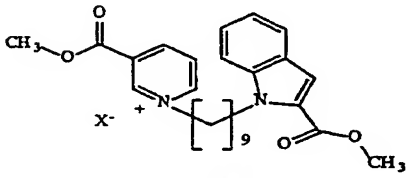

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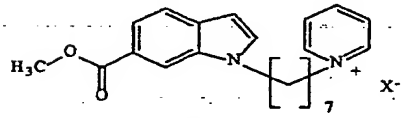

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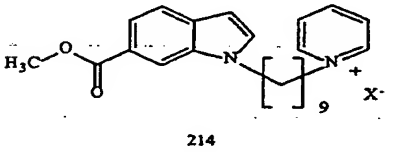

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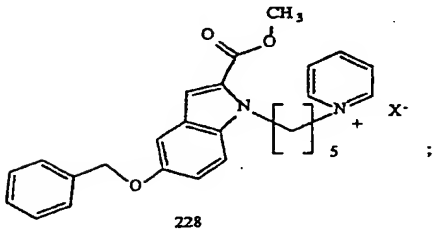

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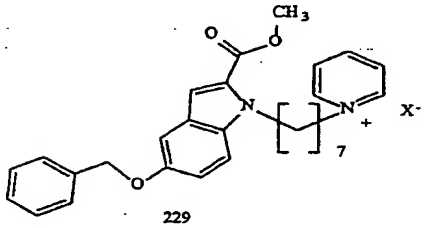

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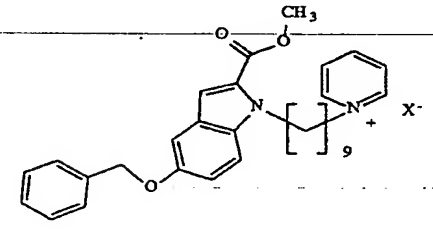

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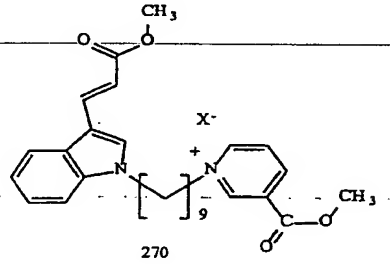

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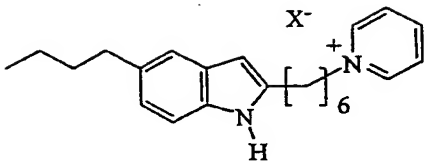

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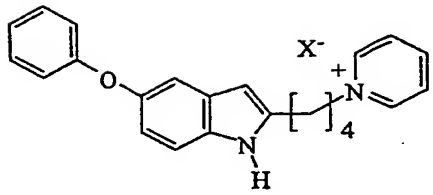

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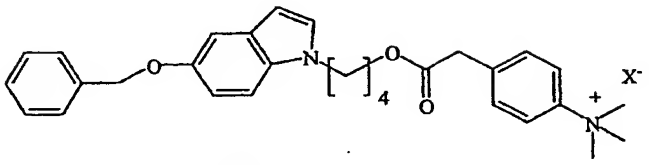

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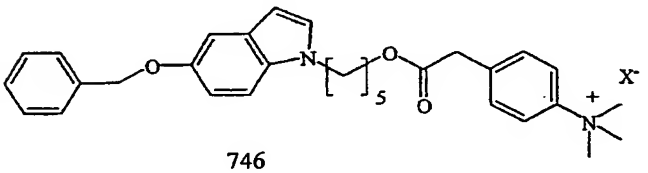

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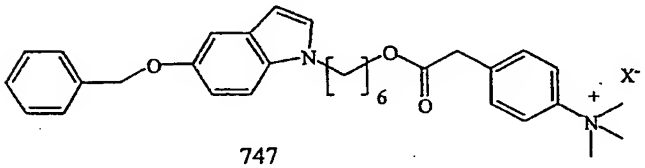

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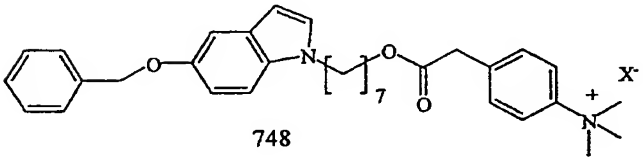

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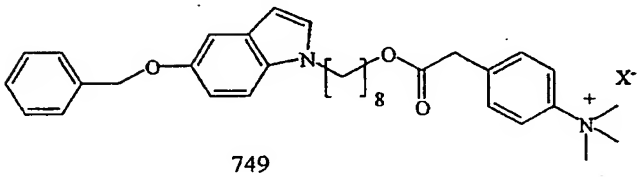

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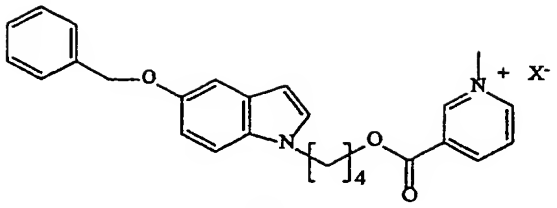

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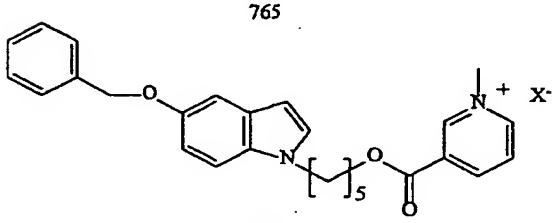

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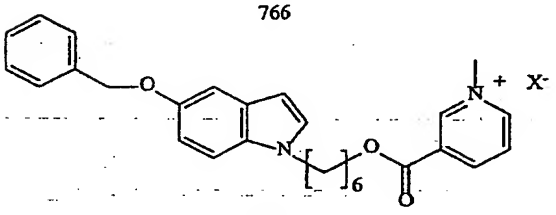

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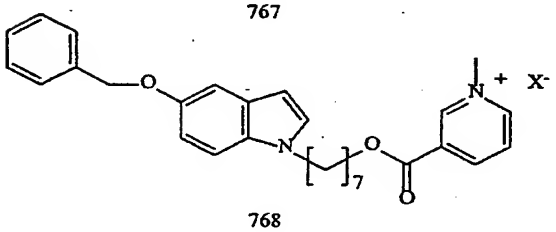

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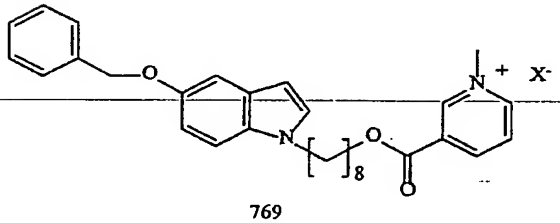

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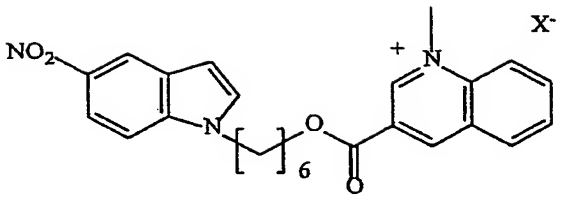

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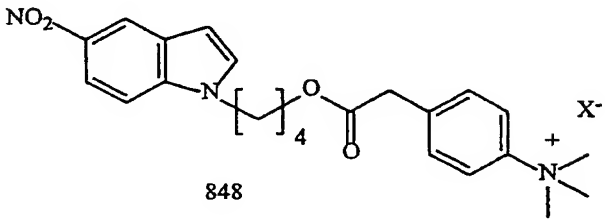

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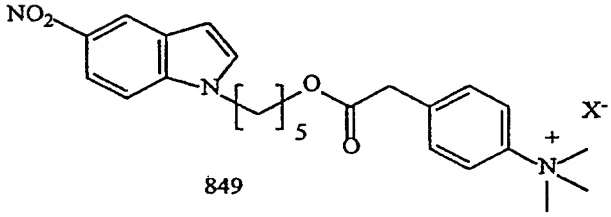

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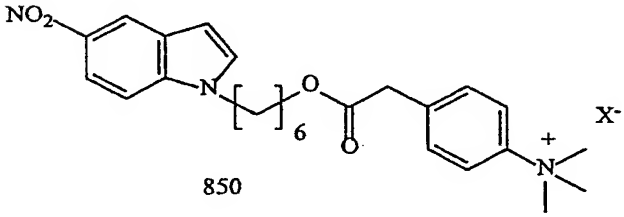

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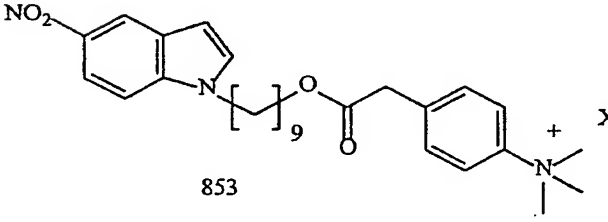

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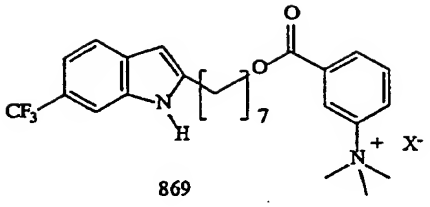

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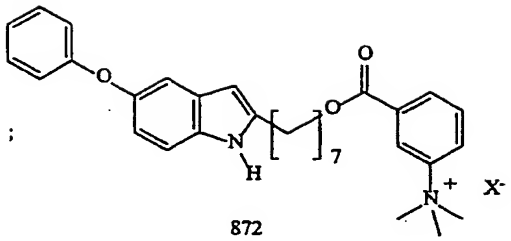

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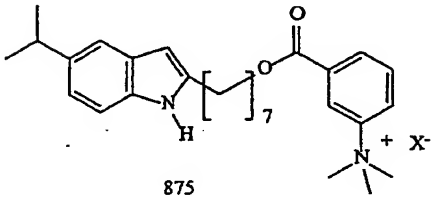

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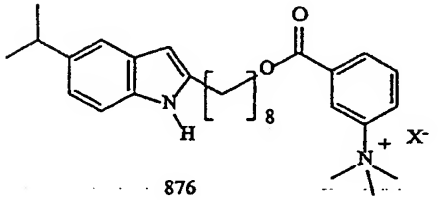

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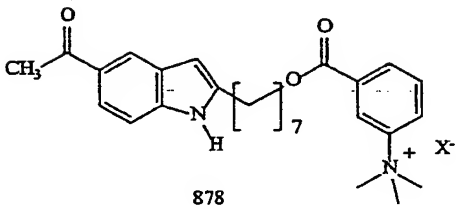

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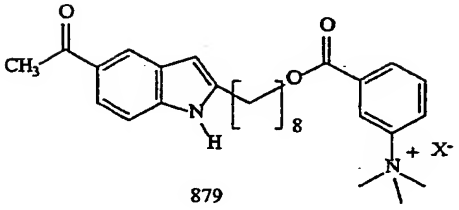

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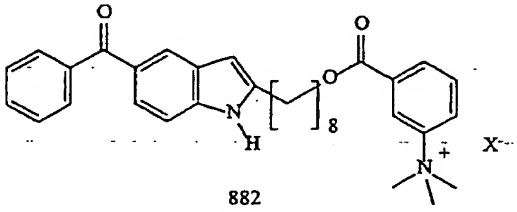

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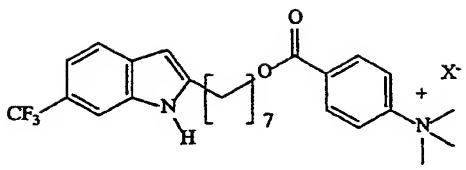

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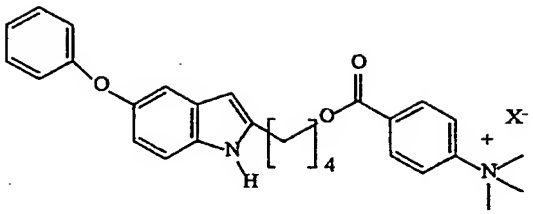

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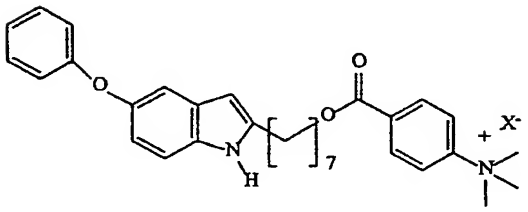

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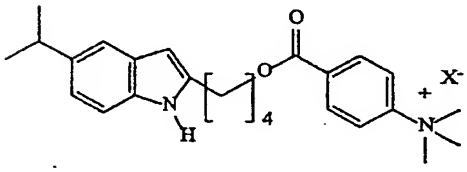

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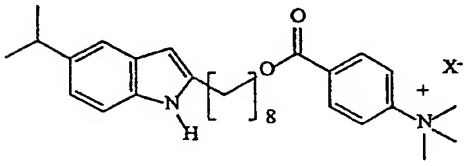

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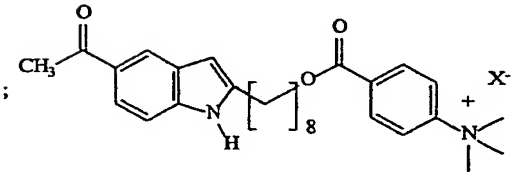

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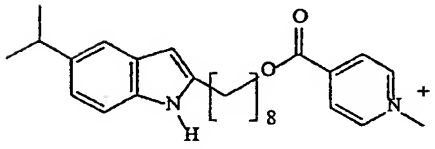

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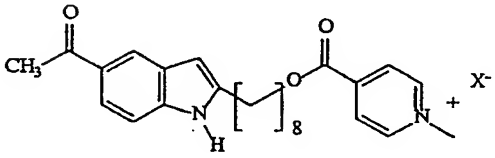

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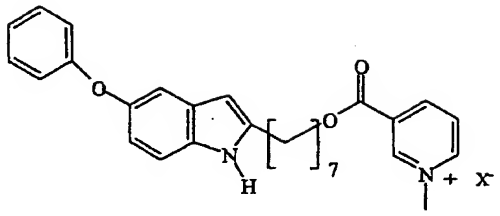

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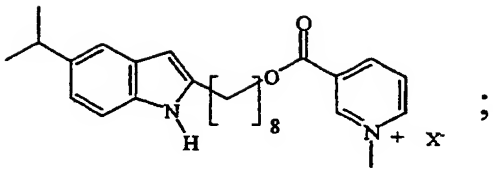

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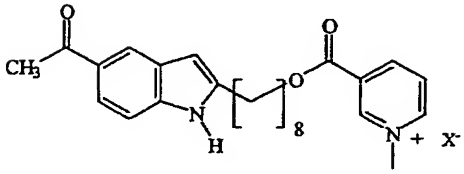

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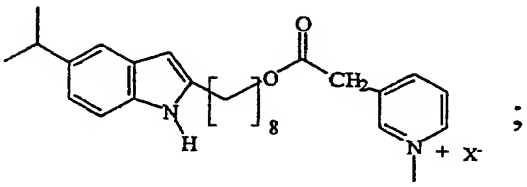

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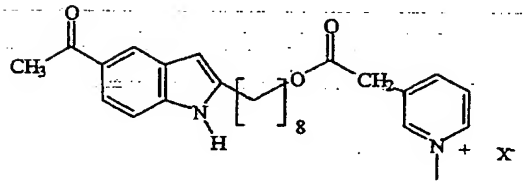

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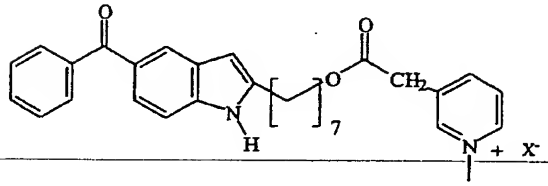

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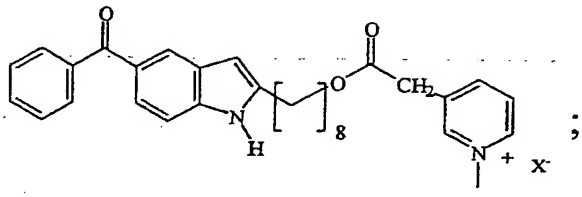

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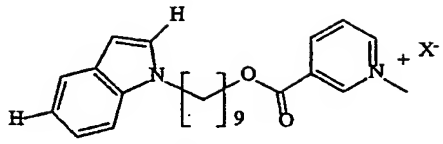

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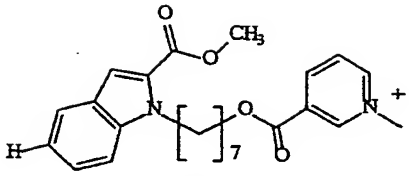

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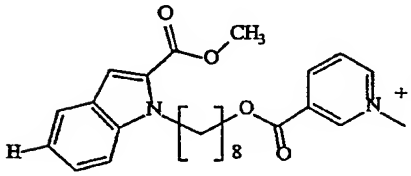

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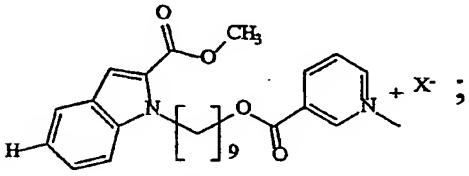

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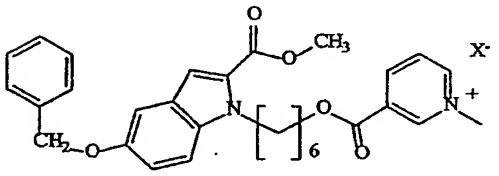

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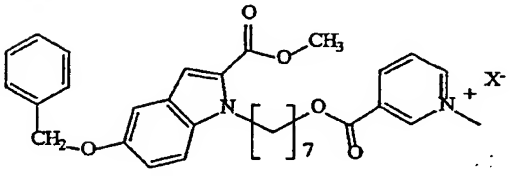

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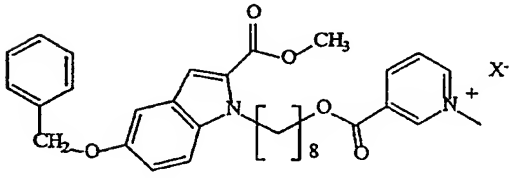

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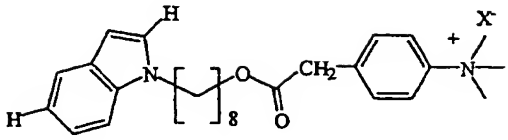

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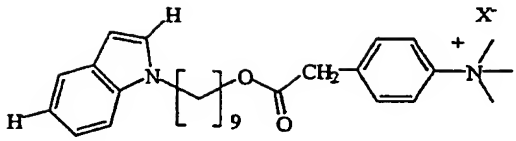

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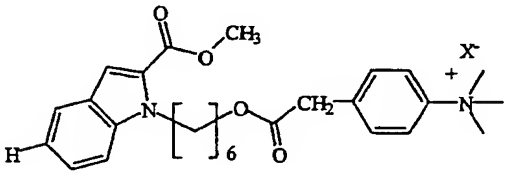

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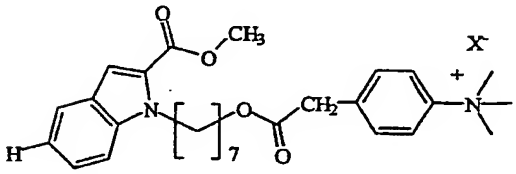

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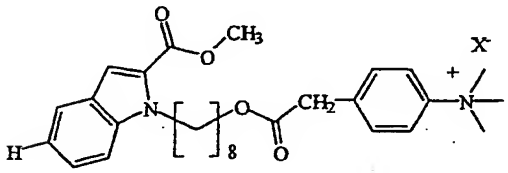

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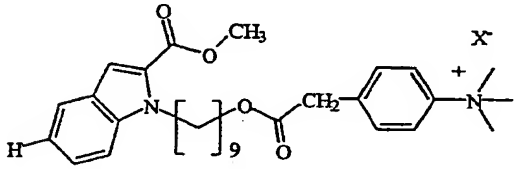

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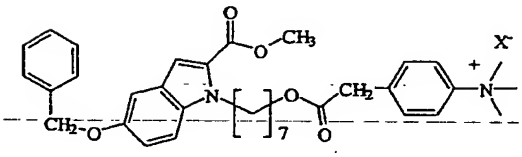

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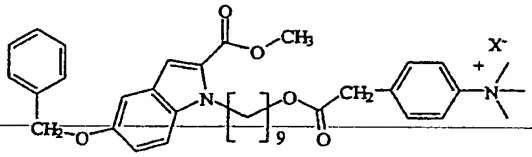

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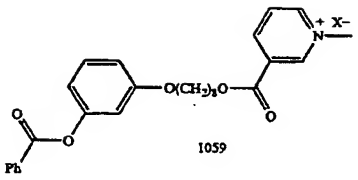
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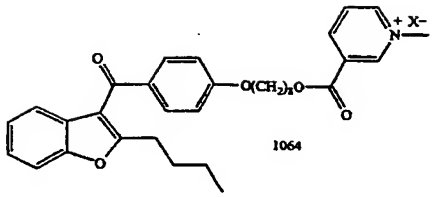
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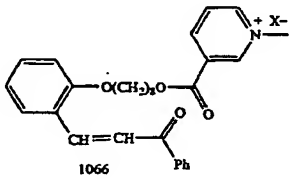
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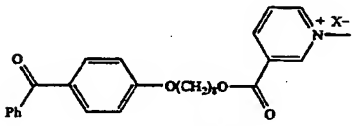
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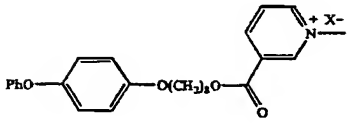
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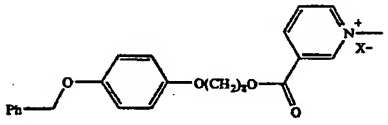
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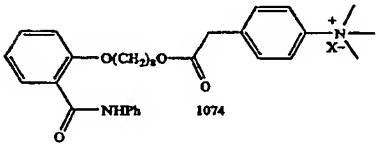
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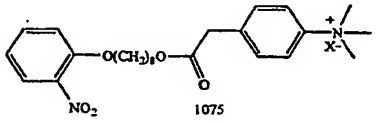
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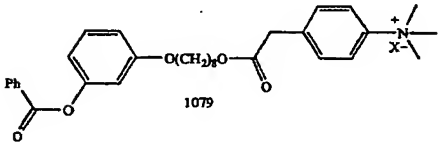
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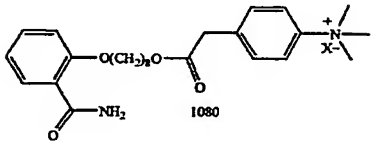
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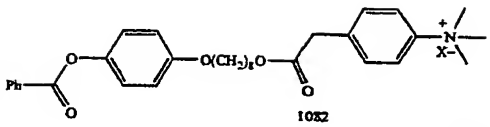

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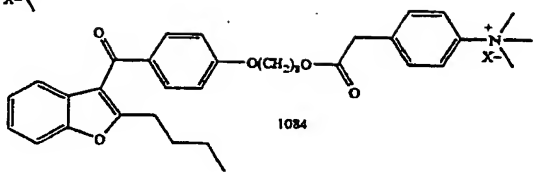

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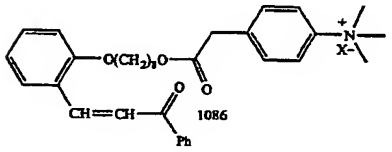

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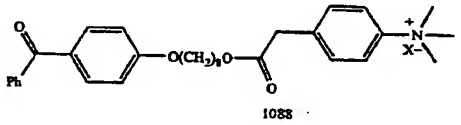

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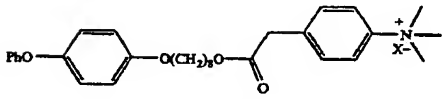

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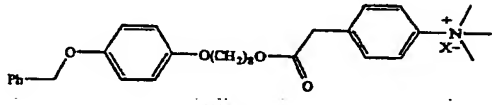

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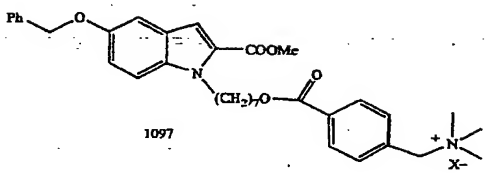

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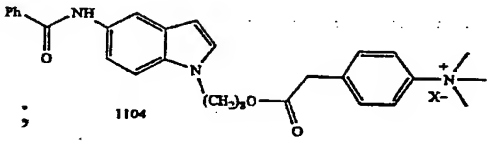

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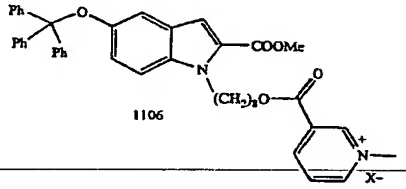

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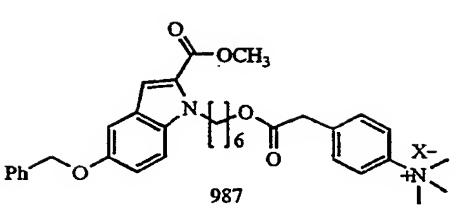

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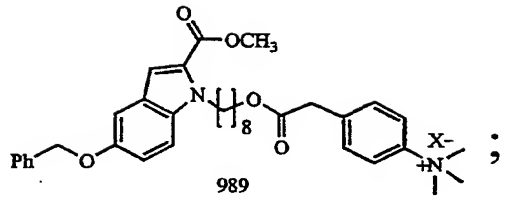

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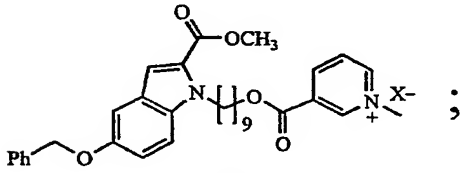

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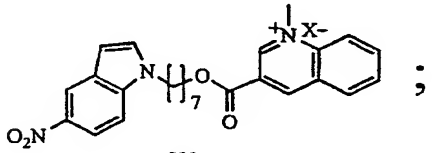

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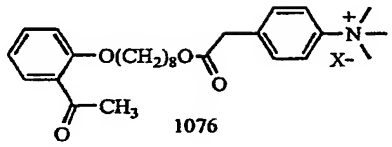
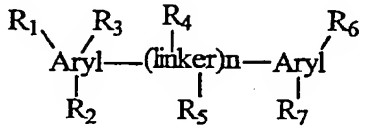


1076 .

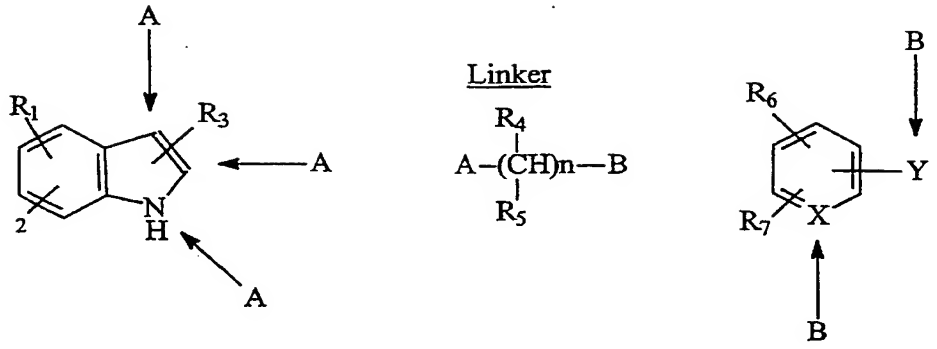
4. The method of Claim 1 wherein the compound administered has Structure 2:



Structure 2

wherein n is an integer of from 1 to 12, R_1 - R_7 each, independently, is an H, an unsubstituted or a substituted cyclic or aliphatic group, or a branched or an unbranched group, and wherein the linker is a cyclic or aliphatic, branched or an unbranched alkyl, alkenyl, or an alkynyl group and wherein the linker may also contain heteroatoms.

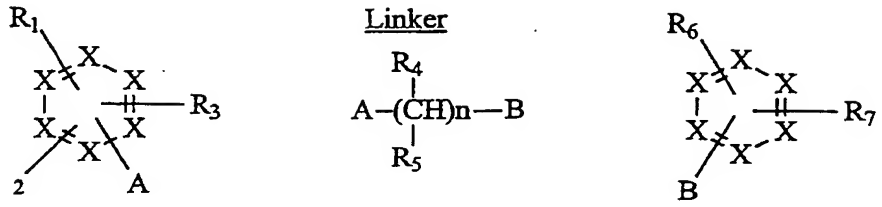
5. The method of Claim 4 wherein n is an integer of from 3 to 10.
6. The method of Claim 4 wherein n is an integer of from 5 to 9.
7. The method of Claim 4 wherein n is an integer of from 6 to 9.
8. The method of Claim 4 wherein R_1 - R_7 each, independently, is an H, alkyl, alkenyl, alknyl, or an aryl group.
9. The method of Claim 4 wherein R_1-R_7, each, independently, is a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups.
10. The method of Claim 1 wherein the compound administered has Structure 4:



Structure 4

wherein X is a C, N, O or S within a monocyclic or bicyclic moiety, A and B represent the respective sites of attachment for the linker, n is an integer of from 1 to 12, R_1-R_7 each, independently, is an H, an unsubstituted or a substituted cyclic group, or an aliphatic group, or a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic group or an aliphatic branched or unbranched alkyl, alkenyl or alkynyl group, and wherein the linker may also contain heteroatoms.

11. The method of Claim 10 wherein n is an integer of from 3 to 10.
12. The method of Claim 10 wherein n is an integer of from 5 to 9.
13. The method of Claim 10 wherein n is an integer of from 6 to 9.
14. The method of Claim 10 wherein R_1-R_7 each, independently, is an H, alkyl, alkenyl, alkynyl, or an aryl group.
15. The method of Claim 10 wherein R_1-R_7 each, independently, is a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups.
16. The method of Claim 1 wherein the compound administered has Structure 6:

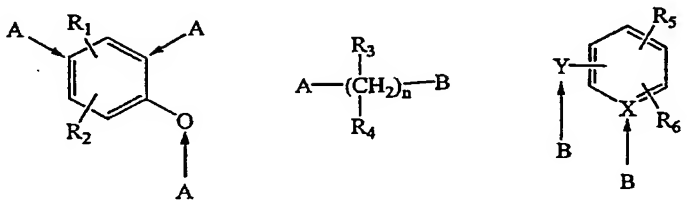


Structure 6

wherein X is C, N, O or S, Y is C, N, O, S, carboxy, ester, amide, or ketone, A and B represent the respective sites of attachment for a linker, n is an integer of from 1 to 12, and R_1-R_7 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic or aliphatic group, branched or unbranched alkyl, alkenyl, or alkynyl group and wherein the linker may also contain heteroatoms.

17. The method of Claim 16 wherein n is an integer of from 3 to 10.
18. The method of Claim 16 wherein n is an integer of from 5 to 9.
19. The method of Claim 16 wherein n is an integer of from 6 to 9.
20. The method of Claim 16 wherein R_1-R_7 each, independently, is an H, alkyl, alkenyl, or alkynyl, or an aryl group.
21. The method of Claim 16 wherein R_1-R_7 each, independently, is an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen and the common derivatives of these groups.

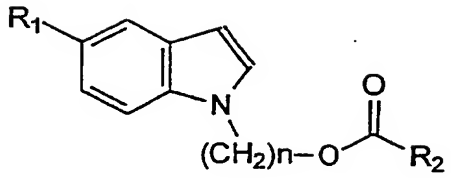
22. The method of Claim 1 wherein the compound administered has Structure 7:



Structure 7

wherein X is C, N, O or S, Y is C, N, O, S, carboxy, ester, amide, or ketone, A and B represent the respective sites of attachment for a linker, n is an integer of from 1 to 12, and R_1-R_6 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, and the linker is a saturated or unsaturated cyclic or aliphatic group, branched or unbranched alkyl, alkenyl, or alkynyl group and wherein the linker may also contain heteroatoms.

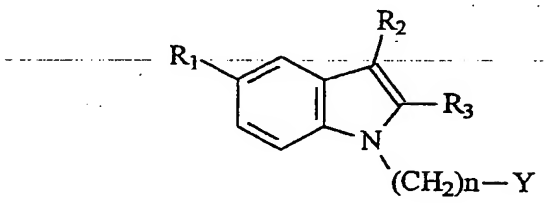
23. The method of Claim 22 wherein n is an integer of from 3 to 10.
24. The method of Claim 22 wherein n is an integer of from 5 to 9.
25. The method of Claim 22 wherein n is an integer of from 6 to 9.
26. The method of Claim 22 wherein R_1-R_6 each, independently, is an H, alkyl, alkenyl, or alkynyl, or an aryl group.
27. The method of Claim 22 wherein R_1-R_6 each, independently, is an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen and the common derivatives of these groups.
28. The method of Claim 1 wherein the compound administered has Structure 8:



Structure 8

wherein n is an integer of from 1 to 12, R_1 is an H, methoxy, benzyloxy, or nitro and R_2 is 3-pyridyl, N-methyl-3-pyridyl, 3-quinolinyl, N-methyl-3-quinolinyl, 3-(dimethylamino)phenyl, 3-(trimethylammonio)phenyl, 4-(dimethylamino)phenyl, 4-(trimethylammonio)phenyl, 4-(dimethylamino)phenylmethyl, or 4-(trimethylammonio)phenylmethyl.

29. The method of Claim 28 wherein n is an integer of from 3 to 10.
30. The method of Claim 28 wherein n is an integer of from 5 to 9.
31. The method of Claim 28 wherein n is an integer of from 6 to 9.
32. The method of Claim 1 wherein the compound administered has Structure 10:



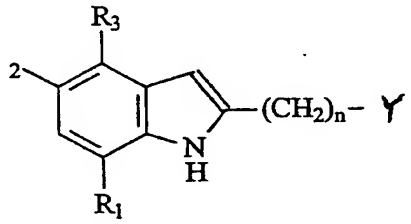
Structure 10

wherein n is an integer of from 1 to 12, R_1 is an H, CO_2H, $-OCH_3$, or $-OCH_2Ph$, R_2 is H, CO_2H, or $CH=CHCO_2H$, R_3 is H or CO_2H, and Y is N-linked pyridine-3-carboxylic acid, N-linked pyridine, N-linked quinoline, or N-linked isoquinoline.

33. The method of Claim 32 wherein n is an integer of from 3 to 10.
34. The method of Claim 32 wherein n is an integer of from 5 to 9.

35. The method of Claim 32 wherein n is an integer of from 6 to 9.

36. The method of Claim 1 wherein the compound administered has Structure 12:



Structure 12

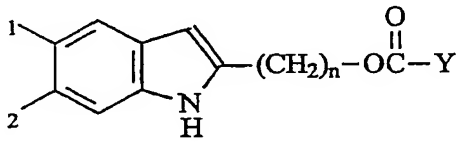
wherein n is an integer of from 1 to 12, R_1 is H, F, or NO_2, R_2 is H, CH_3, CF_3, NO_2, phenyl, n-butyl, isopropyl, F, phenyloxy, triphenylmethyl, methoxycarbonyl, methoxy, carboxy, acetyl, or benzoyl, R_3 is H or CF_3 and Y is N-linked pyridine-3-carboxylic acid, N-linked pyridine, N-linked quinoline, or N-linked isoquinoline.

37. The method of Claim 36 wherein n is an integer of from 3 to 10.

38. The method of Claim 36 wherein n is an integer of from 5 to 9.

39. The method of Claim 36 wherein n is an integer of from 6 to 9.

40. The method of Claim 1 wherein the compound administered has Structure 14:

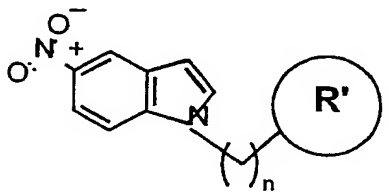


Structure 14

wherein n is an integer of from 1 to 12, R_1 is H, phenyloxy, isopropyl, acetyl, or benzoyl, R_2 is H or CF_3, and Y is 3-(dimethylamino)phenyl, 3-(trimelthylammonio)phenyl, 4-(dimethylamino)phenyl, 4-

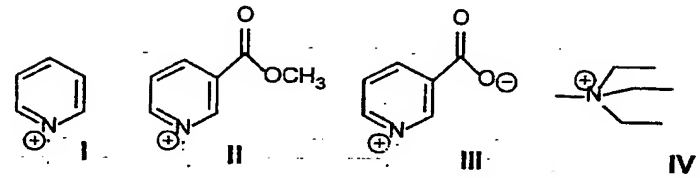
(trimethylammonio)phenyl, 2-(phenyl)phenyl, diphenylmethyl, 3-pyridyl, 4-pyridyl, or pyridine-3-methyl.

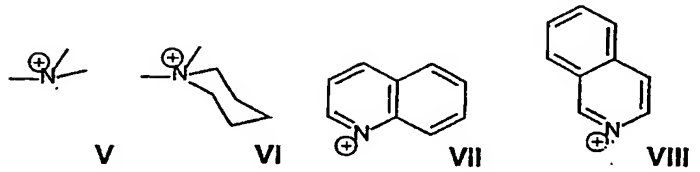
41. The method of Claim 40 wherein n is an integer of from 3 to 10.
42. The method of Claim 40 wherein n is an integer of from 5 to 9.
43. The method of Claim 40 wherein n is an integer of from 6 to 9.
44. The method of Claim 1 wherein the compound administered has Structure 100:

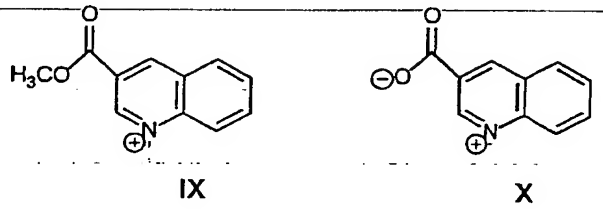


Structure 100

wherein R' is:

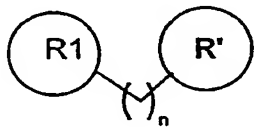






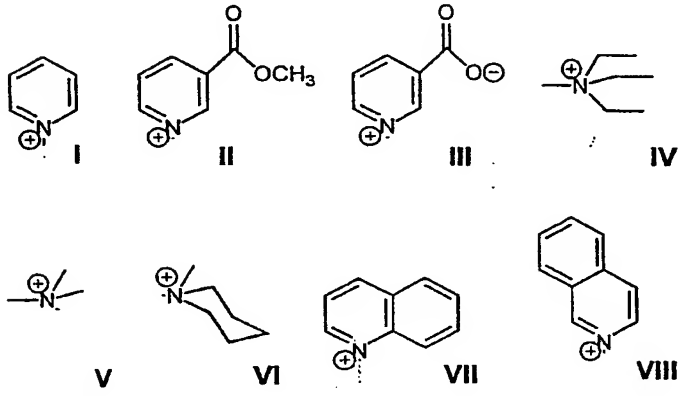
and n is an integer of from 1 to 12.

45. The method of Claim 44 wherein n is an integer of from 3 to 10.
46. The method of Claim 44 wherein n is an integer of from 5 to 9.
47. The method of Claim 44 wherein n is an integer of from 6 to 9.
48. The method of Claim 1 wherein the compound administered has Structure 101:

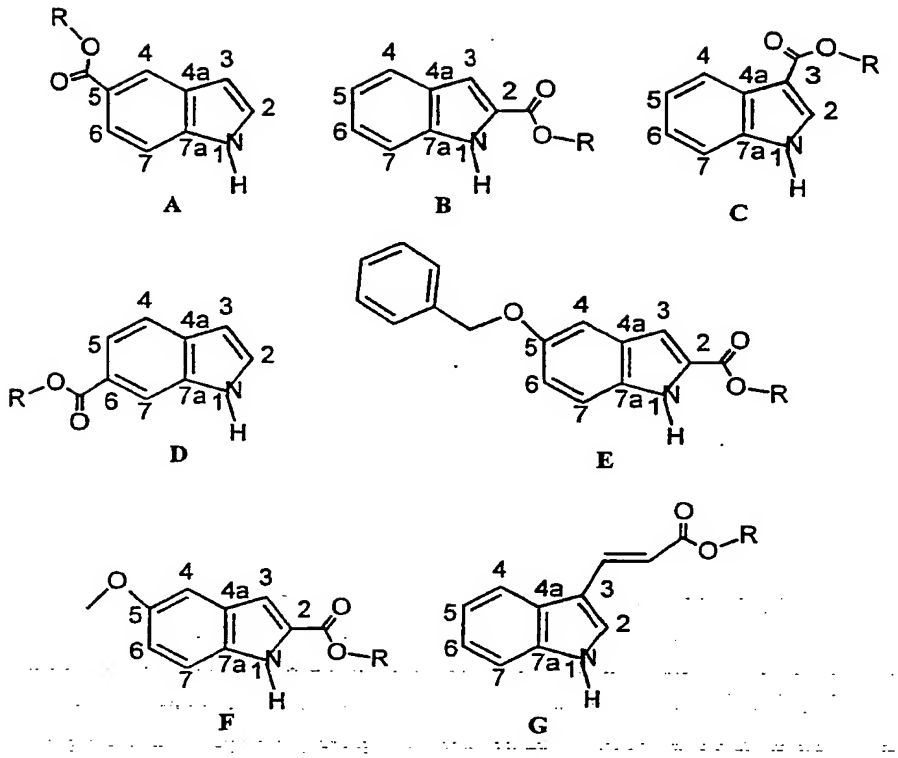


Structure 101

wherein R' is:



wherein R1 is:



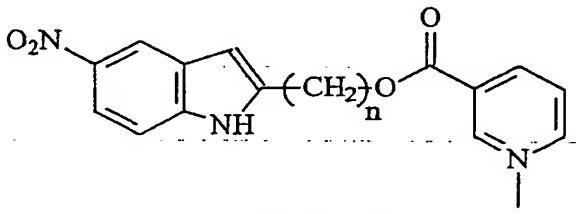
wherein the R group in Fragments A-G is a benzyl group, a methyl group or a hydrogen and wherein n is an integer of from 1 to 12.

49. The method of Claim 48 wherein n is an integer of from 3 to 10.

50. The method of Claim 48 wherein n is an integer of from 5 to 9.

51. The method of Claim 48 wherein n is an integer of from 6 to 9.

52. The method of Claim 1 wherein the compound administered has Structure 130:

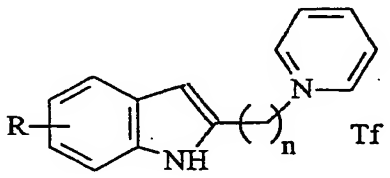


I

Structure 130

wherein n is an integer of from 1 to 12.

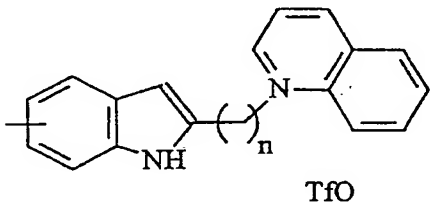
53. The method of Claim 52 wherein n is an integer of from 3 to 10.
54. The method of Claim 52 wherein n is an integer of from 5 to 9.
55. The method of Claim 52 wherein n is an integer of from 6 to 9.
56. The method of Claim 1 wherein the compound administered has Structure 132:



Structure 132

wherein n is an integer of from 1 to 12 and R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$ or 5-COOH.

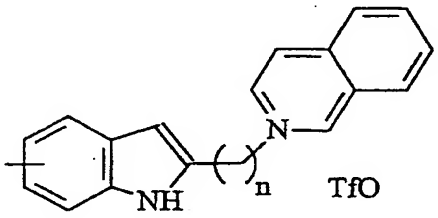
57. The method of Claim 56 wherein n is an integer of from 3 to 10.
58. The method of Claim 56 wherein n is an integer of from 5 to 9.
59. The method of Claim 56 wherein n is an integer of from 6 to 9.
60. The method of Claim 1 wherein the compound administered has Structure 134:



Structure 134

wherein n is an integer of from 1 to 12 and R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$, or 5-COOH.

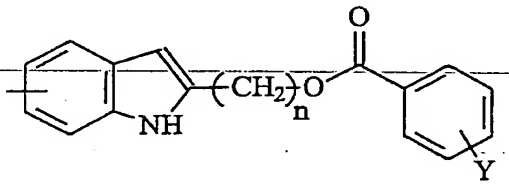
61. The method of Claim 60 wherein n is an integer of from 3 to 10.
62. The method of Claim 60 wherein n is an integer of from 5 to 9.
63. The method of Claim 60 wherein n is an integer of from 6 to 9.
64. The method of Claim 1 wherein the compound administered has Structure 136:



Structure 136

wherein n is an integer of from 1 to 12 and R is 5-H, 6-CF_3, 5-CH_3, 5,7-diF, 5,7-diNO_2, 5-Butyl, 5-iPropyl, 5-Phenyl, 5-NO_2, 5-Trityl, 5-F, 5-OPh, 5-COPh, 5-CF_3, 5-$COCH_3$, 5-OCH_3, 5-$COOCH_3$, or 5-COOH.

65. The method of Claim 64 wherein n is an integer of from 3 to 10.
66. The method of Claim 64 wherein n is an integer of from 5 to 9.
67. The method of Claim 64 wherein n is an integer of from 6 to 9.
68. The method of Claim 1 wherein the compound administered has Structure 138:

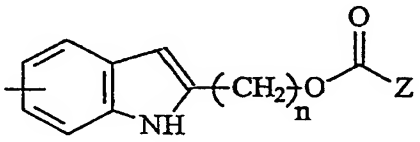


Structure 138

wherein n is an integer of from 1 to 12 and R is 5-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh and Y is 3-N,N-dimethylamino(phenyl), 4-N,N-

dimethylamino(phenyl), or 2-Ph.

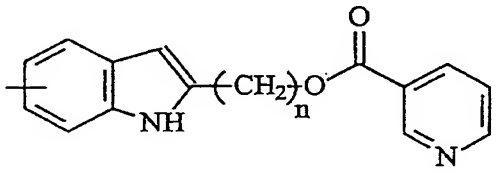
69. The method of Claim 68 wherein n is an integer of from 3 to 10.
70. The method of Claim 68 wherein n is an integer of from 5 to 9.
71. The method of Claim 68 wherein n is an integer of from 6 to 9.
72. The method of Claim 1 wherein the compound administered has Structure 140:



Structure 140

wherein n is an integer of from 1 to 12, R is 5-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$ or 5-COPh, and Z is $CH(Ph)_2$ or 3-Pyridyl.

73. The method of Claim 72 wherein n is an integer of from 3 to 10.
74. The method of Claim 72 wherein n is an integer of from 5 to 9.
75. The method of Claim 72 wherein n is an integer of from 6 to 9.
76. The method of Claim 1 wherein the compound administered has Structure 142:

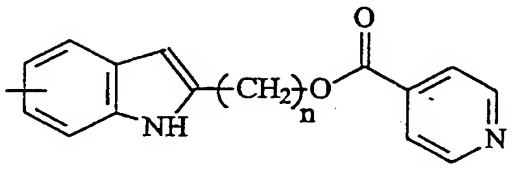


Structure 142

wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh.

77. The method of Claim 76 wherein n is an integer of from 3 to 10.
78. The method of Claim 76 wherein n is an integer of from 5 to 9.
79. The method of Claim 76 wherein n is an integer of from 6 to 9.

80. The method of Claim 1 wherein the compound administered has Structure 144:



Structure 144

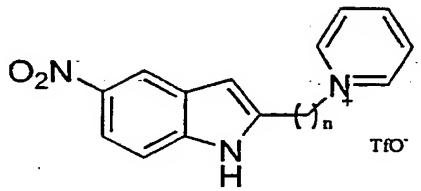
wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-iPropyl, 5-$COCH_3$, or 5-COPh.

81. The method of Claim 80 wherein n is an integer of from 3 to 10.

82. The method of Claim 80 wherein n is an integer of from 5 to 9.

83. The method of Claim 80 wherein n is an integer of from 6 to 9.

84. The method of Claim 1 wherein the compound administered has Structure 146:



Structure 146

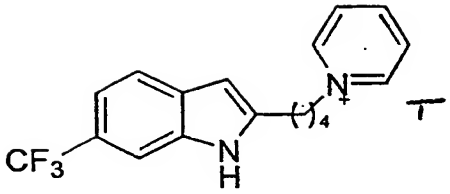
wherein n is an integer of from 1 to 12.

85. The method of Claim 84 wherein n is an integer of from 3 to 10.

86. The method of Claim 84 wherein n is an integer of from 5 to 9.

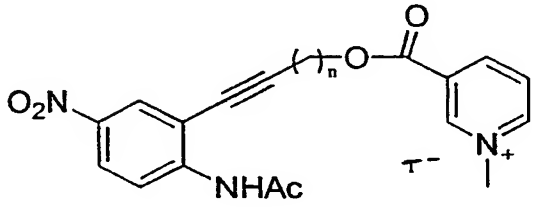
87. The method of Claim 84 wherein n is an integer of from 6 to 9.

88. The method of Claim 1 wherein the compound administered has Structure 148:



Structure 148.

89. The method of Claim 1 wherein the compound administered has Structure 150:



Structure 150

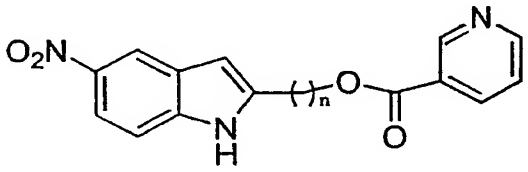
wherein R is an integer of from 1 to 12.

90. The method of Claim 89 wherein n is an integer of from 3 to 10.

91. The method of Claim 89 wherein n is an integer of from 5 to 9.

92. The method of Claim 89 wherein n is an integer of from 6 to 9.

93. The method of Claim 1 wherein the compound administered has Structure 152:



Structure 152

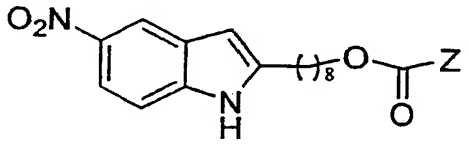
wherein n is an integer of from 1 to 12.

94. The method of Claim 93 wherein n is an integer of from 3 to 10.

95. The method of Claim 93 wherein n is an integer of from 5 to 9.

96. The method of Claim 93 wherein n is an integer of from 6 to 9.

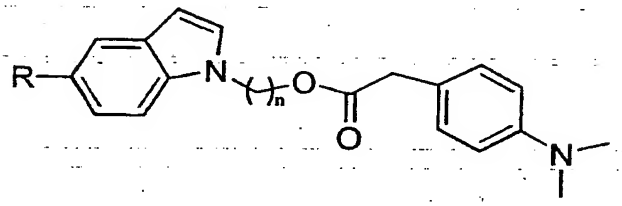
97. The method of Claim 1 wherein the compound administered has Structure 154:



Structure 154

wherein Z is CH(diPh), 4-(N,N-dimethylamino)phenyl, CH_2CH_2-(3-pyridyl), or (2-phenyl)-phenyl.

98. The method of Claim 1 wherein the compound administered has Structure 156:



Structure 156

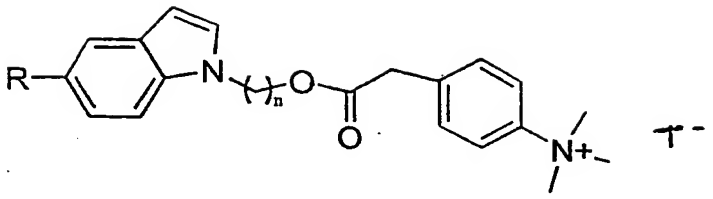
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

99. The method of Claim 98 wherein n is an integer of from 3 to 10.

100. The method of Claim 98 wherein n is an integer of from 5 to 9.

101. The method of Claim 98 wherein n is an integer of from 6 to 9.

102. The method of Claim 1 wherein the compound administered has Structure 158:



Structure 158

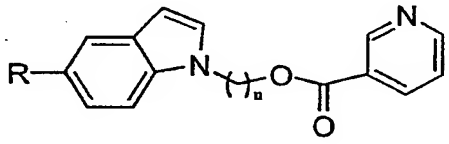
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

103. The method of Claim 102 wherein n is an integer of from 3 to 10.

104. The method of Claim 102 wherein n is an integer of from 5 to 9.

105. The method of Claim 102 wherein n is an integer of from 6 to 9.

106. The method of Claim 1 wherein the compound administered has Structure 160:



Structure 160

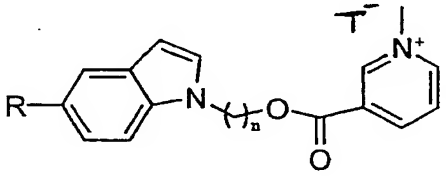
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

107. The method of Claim 106 wherein n is an integer of from 3 to 10.

108. The method of Claim 106 wherein n is an integer of from 5 to 9.

109. The method of Claim 106 wherein n is an integer of from 6 to 9.

110. The method of Claim 1 wherein the compound administered has Structure 162 :



Structure 162

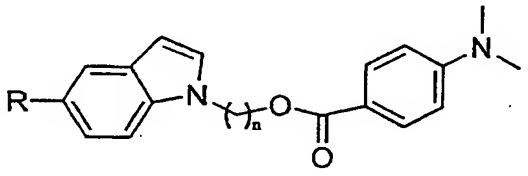
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

111. The method of Claim 110 wherein n is an integer of from 3 to 10.

112. The method of Claim 110 wherein n is an integer of from 5 to 9.

113. The method of Claim 110 wherein n is an integer of from 6 to 9.

114. The method of Claim 1 wherein the compound administered has Structure 164:



Structure 164

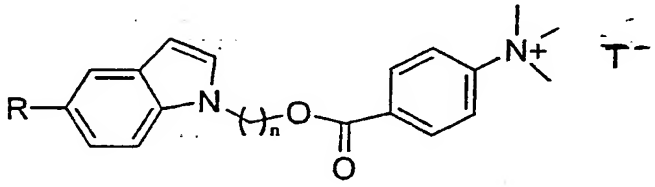
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

115. The method of Claim 114 wherein n is an integer of from 3 to 10.

116. The method of Claim 114 wherein n is an integer of from 5 to 9.

117. The method of Claim 114 wherein n is an integer of from 6 to 9.

118. The method of Claim 1 wherein the compound has Structure 166:



Structure 166

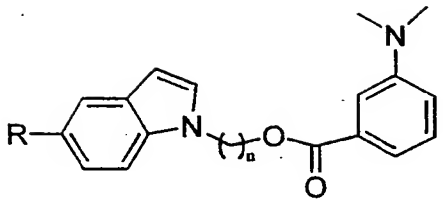
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

119. The method of Claim 118 wherein n is an integer of from 3 to 10.

120. The method of Claim 118 wherein n is an integer of from 5 to 9.

121. The method of Claim 118 wherein n is an integer of from 6 to 9.

122. The method of Claim 1 wherein the compound administered has Structure 168:



Structure 168

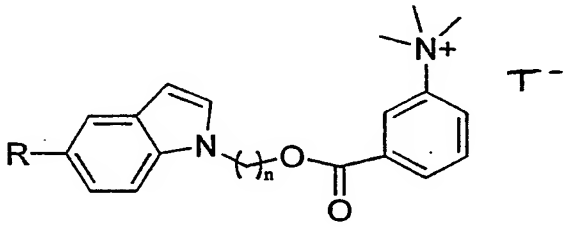
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

123. The method of Claim 122 wherein n is an integer of from 3 to 10.

124. The method of Claim 122 wherein n is an integer of from 5 to 9.

125. The method of Claim 122 wherein n is an integer of from 6 to 9.

126. The method of Claim 1 wherein the compound administered has Structure 170:



Structure 170

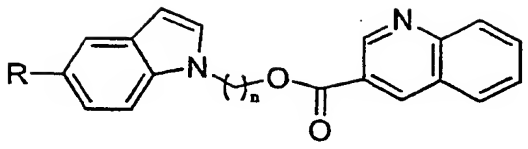
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

127. The method of Claim 126 wherein n is an integer of from 3 to 10.

128. The method of Claim 126 wherein n is an integer of from 5 to 9.

129. The method of Claim 126 wherein n is an integer of from 6 to 9.

130. The method of Claim 1 wherein the compound administered has Structure 172:



Structure 172

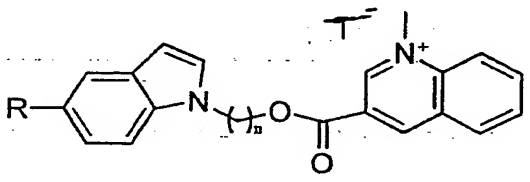
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

131. The method of Claim 130 wherein n is an integer of from 3 to 10.

132. The method of Claim 130 wherein n is an integer of from 5 to 9.

133. The method of Claim 130 wherein n is an integer of from 6 to 9.

134. The method of Claim 1 wherein the compound administered has Structure 174:



Structure 174

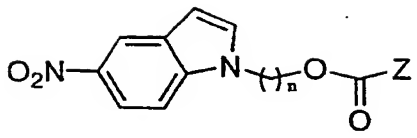
wherein n is an integer of from 1 to 12 and R is $-OCH_3$ or $-OCH_2Ph$.

135. The method of Claim 135 wherein n is an integer of from 3 to 10.

136. The method of Claim 135 wherein n is an integer of from 5 to 9.

137. The method of Claim 135 wherein n is an integer of from 6 to 9.

138. The method of Claim 1 wherein the compound administered has Structure 176:



Structure 176

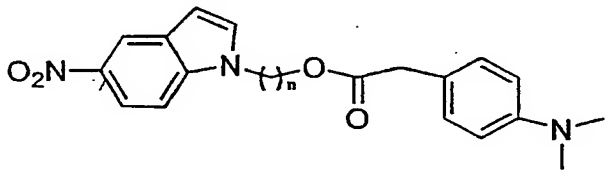
wherein n is an integer of from 1 to 12 and Z is 3-quinoline, 3-(N,N-dimethylamino)phenyl, or 4-(N,N-dimethylamino)phenyl.

139. The method of Claim 138 wherein n is an integer of from 3 to 10.

140. The method of Claim 138 wherein n is an integer of from 5 to 9.

141. The method of Claim 138 wherein n is an integer of from 6 to 9.

142. The method of Claim 1 wherein the compound administered has Structure 178:



Structure 178

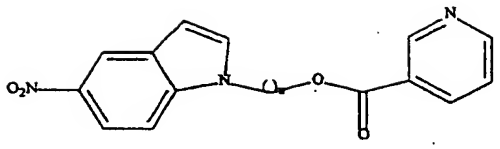
wherein n is an integer of from 1 to 12.

143. The method of Claim 142 wherein n is an integer of from 3 to 10.

144. The method of Claim 142 wherein n is an integer of from 5 to 9.

145. The method of Claim 142 wherein n is an integer of from 6 to 9.

146. The method of Claim 1 wherein the compound administered has Structure 180:



Structure 180

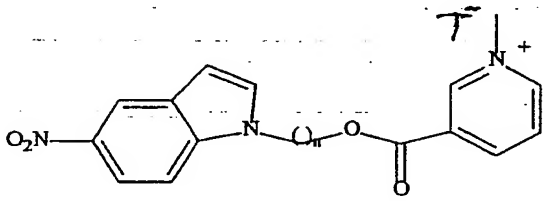
wherein n is an integer of from 1 to 12.

147. The method of Claim 146 wherein n is an integer of from 3 to 10.

148. The method of Claim 146 wherein n is an integer of from 5 to 9.

149. The method of Claim 146 wherein n is an integer of from 6 to 9.

150. The method of Claim 1 wherein the compound administered has Structure 182:



Structure 182

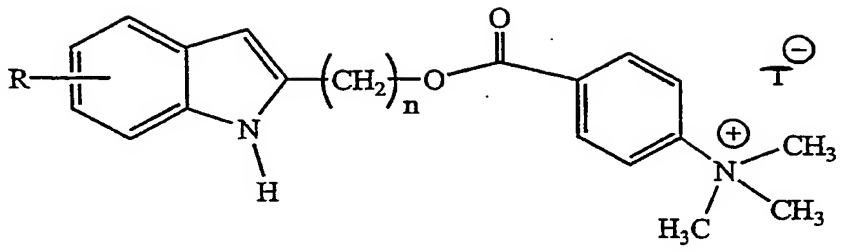
wherein n is an integer of from 1 to 12.

151. The method of Claim 150 wherein n is an integer of from 3 to 10.

152. The method of Claim 150 wherein n is an integer of from 5 to 9.

153. The method of Claim 150 wherein n is an integer of from 6 to 9.

154. The method of Claim 1 wherein the compound administered has Structure 184:



Structure 184

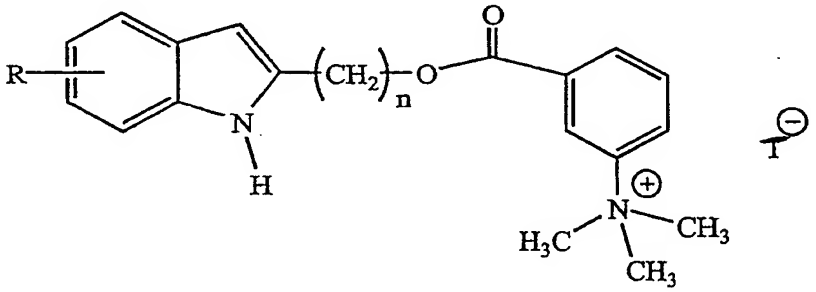
wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh.

155. The method of Claim 154 wherein n is an integer of from 3 to 10.

156. The method of Claim 154 wherein n is an integer of from 5 to 9.

157. The method of Claim 154 wherein n is an integer of from 6 to 9.

158. The method of Claim 1 wherein the compound administered has Structure 186:



Structure 186

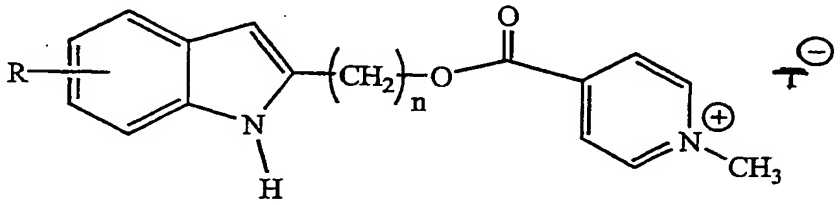
wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh.

159. The method of Claim 158 wherein n is an integer of from 3 to 10.

160. The method of Claim 158 wherein n is an integer of from 5 to 9.

161. The method of Claim 158 wherein n is an integer of from 6 to 9.

162. The method of Claim 1 wherein the compound administered has Structure 188:



Structure 188

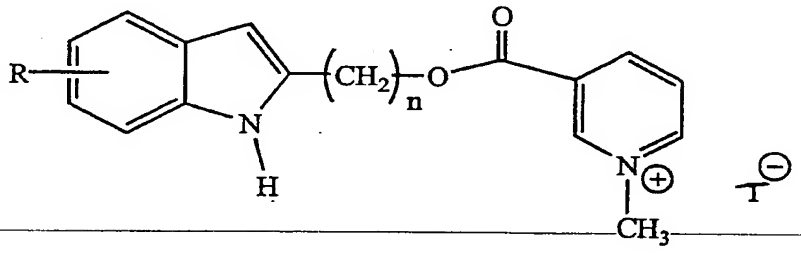
wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh.

163. The method of Claim 162 wherein n is an integer of from 3 to 10.

164. The method of Claim 162 wherein n is an integer of from 5 to 9.

165. The method of Claim 162 wherein n is an integer of from 6 to 9.

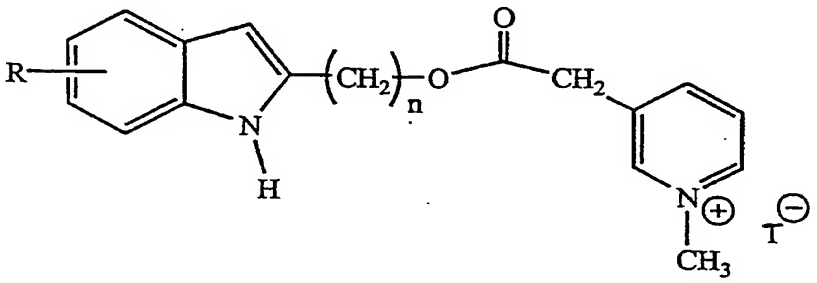
166. The method of Claim 1 wherein the compound administered has Structure 190:



Structure 190

wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh.

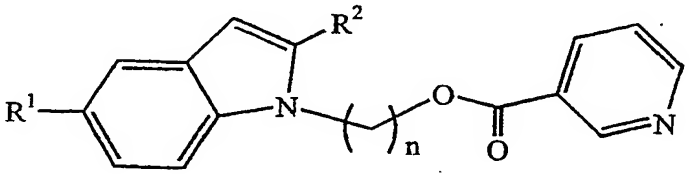
167. The method of Claim 167 wherein n is an integer of from 3 to 10.
168. The method of Claim 167 wherein n is an integer of from 5 to 9.
169. The method of Claim 167 wherein n is an integer of from 6 to 9.
170. The method of Claim 1 wherein the compound administered has Structure 192:



Structure 192

wherein n is an integer of from 1 to 12 and R is 6-CF_3, 5-OPh, 5-$CH(CH_3)_2$, 5-$COCH_3$ or 5-COPh.

171. The method of Claim 170 wherein n is an integer of from 3 to 10.
172. The method of Claim 170 wherein n is an integer of from 5 to 9.
173. The method of Claim 170 wherein n is an integer of from 6 to 9.
174. The method of Claim 1 wherein the compound administered has Structure 194:



Structure 194

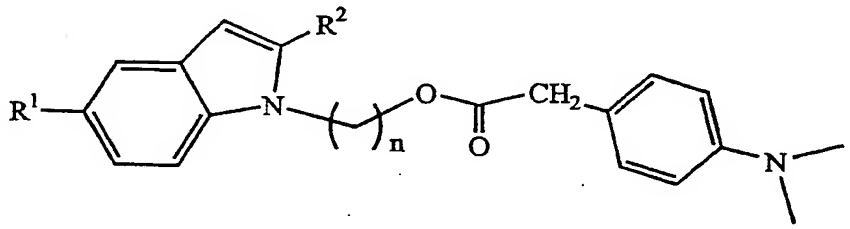
wherein n is an integer of from 1 to 12 and R^1 is an H or -OCH2Ph and R^2 is H or $COOCH_3$.

175. The method of Claim 174 wherein n is an integer of from 3 to 10.

176. The method of Claim 174 wherein n is an integer of from 5 to 9.

177. The method of Claim 174 wherein n is an integer of from 6 to 9.

178. The method of Claim 1 wherein the compound administered has Structure 196:



Structure 196

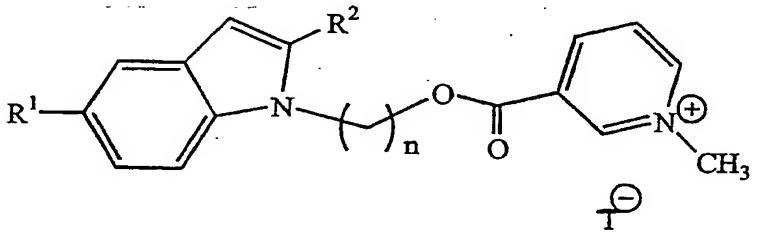
wherein n is an integer of from 1 to 12 and R^1 is H or $-OCH_2Ph$ and R^2 is H or $COOCH_3$.

179. The method of Claim 178 wherein n is an integer of from 2 to 12.

180. The method of Claim 178 wherein n is an integer of from 5 to 9.

181. The method of Claim 178 wherein n is an integer of from 6 to 9.

182. The method of Claim 1 wherein the compound administered has Structure 198:



Structure 198

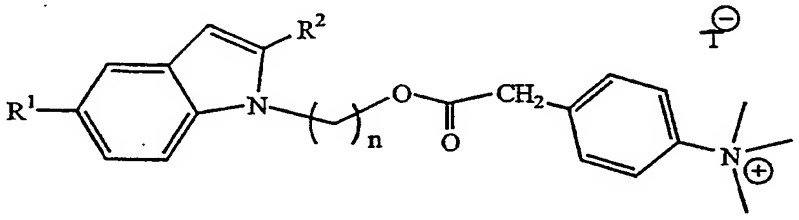
wherein n is an integer of from 1 to 12, and R^1 is H, $-OCH_2Ph$, or $OCPh_3$ and R^2 is Hr $COOCH_3$.

183. The method of Claim 182 wherein n is an integer of from 3 to 10.

184. The method of Claim 182 wherein n is an integer of from 5 to 9.

185. The method of Claim 182 wherein n is an integer of from 6 to 9.

186. The method of Claim 1 wherein the compound administered has Structure 200:



Structure 200

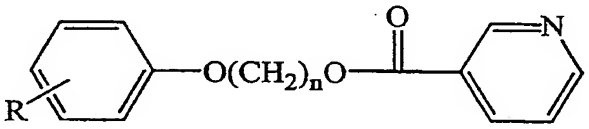
wherein n is an integer of from 1 to 12 and R^1 is H or a -OCH_2Ph and R^2 is H or $COOCH_3$.

187. The method of Claim 186 wherein n is an integer of from 3 to 10.

188. The method of Claim 186 wherein n is an integer of from 5 to 9.

189. The method of Claim 186 wherein n is an integer of from 6 to 9.

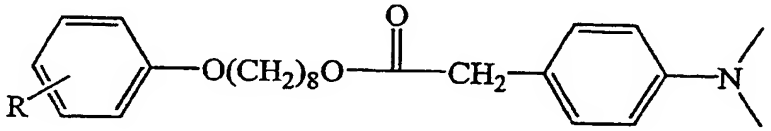
190. The method of Claim 1 wherein the compound administered has Structure 202A:



Structure 202A

wherein n is an integer of from 1 to 12 and wherein R is H; 4-NO_2; 2-CONHPh; 2-NO_2; 4-[1'(4'-acetylpiperazine)]; 2-$COCH_3$; 3-$OCOCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 4-[5'-(5'-phenylhydantoin)]; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 4-$CONH_2$; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); 3-(N-morpholine); 2-(N-pyrrolidine); 2-(N-morpholine); or 4-OCH_2Ph.

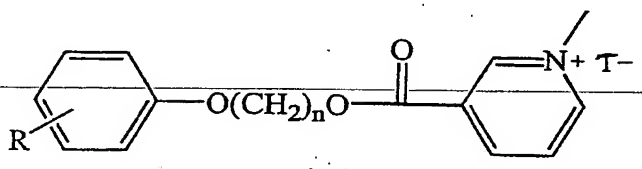
191. The method of Claim 190 wherein n is an integer of from 3 to 10.
192. The method of Claim 190 wherein n is an integer of from 5 to 9.
193. The method of Claim 190 wherein n is an integer of from 6 to 9.
194. The method of Claim 1 wherein the compound administered has Structure 204A:



Structure 204A

wherein n is an integer of from 1 to 12 and wherein R is H; 4-NO_2; 2-CONHPh; 2-NO_2; 4-[1'(4'-acetylpiperazine)]; 2-$COCH_3$; 3-$OCOCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 4-[5'-(5'-phenylhydantoin)]; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 4-$CONH_2$; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); 3-(N-morpholine); 2-(N-pyrrolidine); 2-(N-morpholine); or 4-OCH_2Ph.

195. The method of Claim 194 wherein n is an integer of from 3 to 10.
196. The method of Claim 194 wherein n is an integer of from 5 to 9.
197. The method of Claim 194 wherein n is an integer of from 6 to 9.
198. The method of Claim 1 wherein the compound administered has Structure 206:



Structure 206

wherein n is an integer of from 1 to 12 and R is H; 4-NO_2; 2-CONHPh; 2-NO_2; 2-$COCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 2-

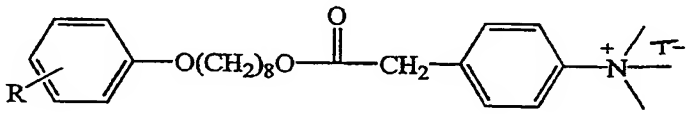
CH=CHCOPh; 2-OCH_3; 4-COPh; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); or 4-OCH_2Ph.

199. The method of Claim 198 wherein n is an integer of from 3 to 10.

200. The method of Claim 198 wherein n is an integer of from 5 to 9.

201. The method of Claim 198 wherein n is an integer of from 6 to 9.

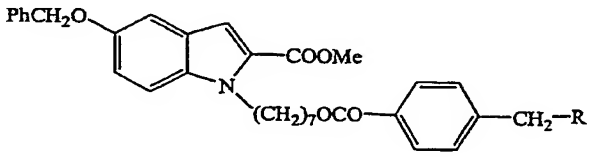
202. The method of Claim 1 wherein the compound administered has Structure 208:



Structure 208

wherein R is 4-NO_2; 2-CONHPh; 2-NO_2; 2-$COCH_3$; 3-OCH_3; 4-$COCH_3$; 3-OCOPh; 2-$CONH_2$; 4-CH=CHCOCH$_3$; 4-OCOPh; 4-CH=CHCOPh; 4-{CO-3'[2'-butylbenzo(b)furan]}; 3-NO_2; 2-CH=CHCOPh; 2-OCH_3; 4-COPh; 3-$COCH_3$; 4-OPh; 4-(N-phthalimide); 3-(N-morpholine); 2-(N-morpholine); or 4-OCH_2Ph.

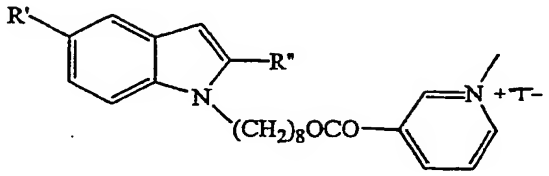
203. The method of Claim 1 wherein the compound administered has Structure 210:



Structure 210

wherein R is NH_2; NMe_2; NMe_3.I; NH_2.HCl; NMe_2 or HCl .

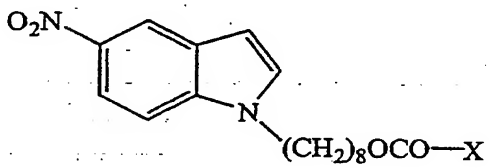
204. The method of Claim 1 wherein the compound administered has Structure 212:



Structure 212

wherein R' is PhCONH or Ph_3C and R'' is H or $COOCH_3$.

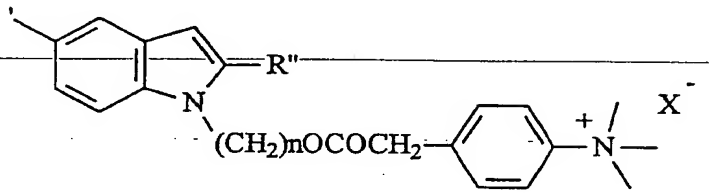
205. The method of Claim 1 wherein the compound administered has Structure 214:



Structure 214

wherein R is 4-hydroxyphenyl or 3-hydroxy-4-methylphenyl.

206. The method of Claim 1 wherein the compound administered has Structure 216:



Structure 216

wherein R' is PhCONH and R" is H or $COOCH_3$ and n is an integer of from 7 to 8.

207. The method of Claim 1 wherein the host is a mammal.

208. The method of Claim 1 wherein the host is a plant.

209. The method of Claim 1 wherein the compound administered has little or no inhibitory effect on the NAD synthetase enzyme of the host.

210. The method of Claim 1 comprising oral, rectal, intramuscularly, intravenous, intravesicular or topical administration.

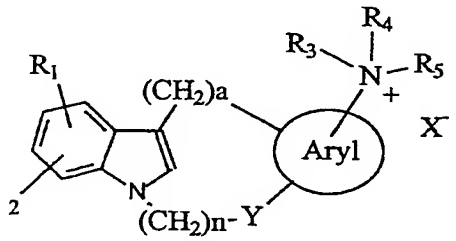
211. The method of Claim 1 wherein the compound is administered in a dosage of between about 0.1 to about 15g per day and wherein the dosage is administered from about 1 to about 4 times per day.

212. A method of killing yeast with an amount of yeast NAD synthetase enzyme inhibitor to reduce or eliminate the production of NAD whereby the yeast is killed.

213. A method of decreasing yeast growth, comprising contacting the yeast with an amount of a yeast NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby yeast growth is decreased.

214. The method of Claim 213 wherein the NAD synthetase enzyme inhibitor is a compound that selectively binds with one or more catalytic sites on a yeast NAD synthetase enzyme to reduce or eliminate the production of NAD by the yeast.

215. The method of Claim 1 wherein the compound administered has Structure 300:



Structure 300

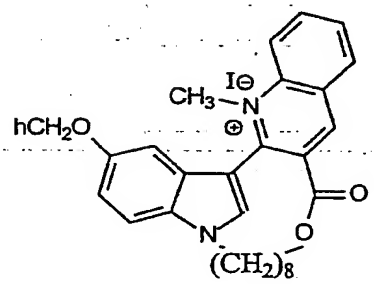
wherein Y is C, N, O, S, ester, amide, or ketone, n is an integer of from 1 to 12, a is an integer from 1-3, and R_1-R_5 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, or alkynyl, or an aryl group while R_1-R_2 may also be an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, ester, sulfonate, halogen, alkoxy, or aryloxy group, and the $(CH_2)_n$ linker may be saturated or unsaturated and contain cyclic or aliphatic groups, branched or unbranched alkyl, alkenyl, or alkynyl substituents, and further wherein the linker may also contain heteroatoms while the aryl group is an aromatic grouping which may contain one or more rings.

216. The method of Claim 215 wherein n is an integer of from 3 to 10.

217. The method of Claim 215 wherein n is an integer of from 5 to 9.

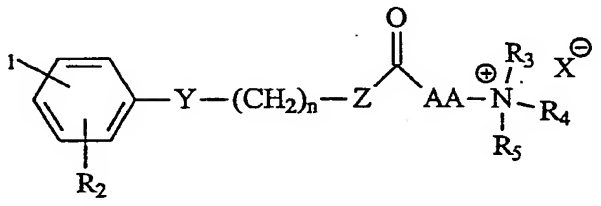
218. The method of Claim 215 wherein n is an integer of from 6 to 9.

219. The method of Claim 1 wherein the compound administered has Structure 1300



1300

220. The method of Claim 1 wherein the compound administered has Structure 400:



Structure 400

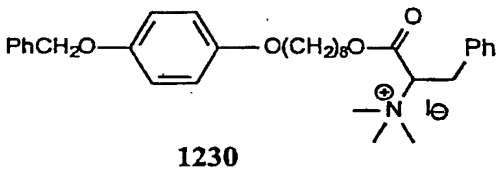
wherein Y is C, N, O, S, ester, amide, or ketone; Z is C, N, O, or S; AA is a natural or unnatural stereoisomer of an α-, β-, γ-, or δ-amino acid in which the carboxyl carbonyl is attached to Z, and the amino grouping may be a primary, secondary, tertiary, or quaternary ammonium compound; n is an integer of from 1 to 12; and R_1-R_5 each, independently, is an H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, or alkynyl, or an aryl group wherein R_1-R_2 may also be an H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, ester, sulfonate, halogen, alkoxy, or aryloxy group and the $(CH_2)_n$ linker may be saturated or unsaturated and contain cyclic or aliphatic groups, branched or unbranched alkyl, alkenyl, or alkynyl substituents, and further wherein the linker may also contain heteroatoms.

221. The method of Claim 220 wherein n is an integer of from 3 to 10.

222. The method of Claim 220 wherein n is an integer of from 5 to 9.

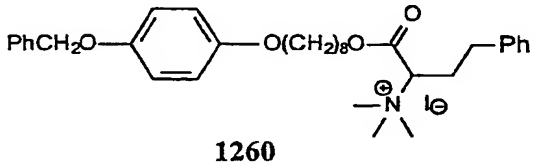
223. The method of Claim 220 wherein n is an integer of from 6 to 9.

224. The method of Claim 1 wherein the compound administered has Structure 1230:



1230

225. The method of Claim 1 wherein the compound administered has Structure 1260:



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